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ORIGINAL ARTICLE

The Impact of Small-for-gestational-age on Neonatal Outcome Among Very-low-birth-weight Infants

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Background: This study aimed to evaluate the impact of small-for-gestational-age (SGA) on mortality and morbidity in very-low-birth-weight (VLBW) infants.
Methods: We conducted a retrospective cohort study on VLBW infants registered at the Premature Baby Foundation of Taiwan between 2007 and 2011. All 21 neonatal departments in Taiwan participated in the data collection, and a total of 4636 VLBW infants were registered during the study period. The SGA group ($n = 560$) was selected from the database on the basis of birth weight below the 10th percentile for gestational age, whereas the appropriate-weight-for-gestational-age (AGA) group ($n = 1120$) included infants randomly selected via incidence density sampling with a 2:1 match for each SGA case. The association of SGA with individual outcome variables including mortality, respiratory distress syndrome, necrotizing enterocolitis, retinopathy of prematurity (ROP), intraventricular hemorrhage, periventricular leukomalacia, and bronchopulmonary dysplasia (BPD) was evaluated after adjustment for potential confounders.
Results: The SGA group was associated with increased risks of mortality [odds ratio (OR) 1.89; 95% confidence interval (CI) 1.39–2.58], severe ROP (OR 1.56; 95% CI 1.13–2.14), and BPD (OR 2.08; 95% CI 1.58–2.75) compared to the AGA group. Further subgroup analysis showed that SGA had significant effects on mortality in the VLBW infants with a gestational age of 24–29

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weeks, as well as on BPD in those with a gestational age of 27—32 weeks. By contrast, the association of SGA with severe ROP was only significant in the VLBW infants with a gestational age of 27—29 weeks.
Conclusion: Our data provide evidence that SGA may be associated with increased risks of neonatal mortality, ROP, and BPD in VLBW infants.

1. Introduction

Small-for-gestational-age (SGA) infants represent a significant percentage of infants admitted to Neonatal Intensive Care Units. SGA is associated with an increased risk of spontaneous and iatrogenic preterm delivery.[1,2] However, its impact on prematurity-associated neonatal morbidity has been disputed due to inconsistent results in the literature. Although some studies showed that SGA was an adverse risk factor of neonatal clinical outcomes,[3,4] others suggested a lower risk for respiratory distress syndrome (RDS) in SGA infants compared to appropriate-weight-for gestational age (AGA) infants.[5—7] Similarly, the reported associations between SGA and risks of intracranial hemorrhage and periventricular leucomalacia (PVL) vary from one study to another.[8,9]

It has been speculated that these discrepancies may be attributed to differences in study methodologies and sample characteristics, such as the definitions of SGA, sample sizes, range of gestational ages, and birth weights of study populations. In addition, AGA comparison groups often differed in either birth weights or gestational age; it was unclear whether the clinical outcome resulted from a shorter gestation period or impaired prenatal growth. To address this issue, some studies have compared the clinical outcomes in SGA infants with those in gestational age-matched AGA infants.[10,11]

To evaluate the association of SGA with neonatal mortality and morbidity accurately, we conducted a matched group study to avoid selection bias and compared the neonatal outcomes in SGA and AGA very-low-birth-weight (VLBW) infants matched for gestational age.

2. Methods

2.1. Ethics statement

Written informed consent was obtained from designated relatives of each infant. The study was approved by the Institutional Review Boards of each participating hospital, including the National Taiwan University Hospital, Chang Gung Memorial Hospital, China Medical University Hospital, National Cheng Kung University Hospital, Tri-Service General Hospital, Chung Shan Medical University Hospital, Shin Kong Wu Ho-Su Memorial Hospital, and Kaohsiung Medical University Chung-Ho Memorial Hospital, as well as the Joint Institutional Review Board of the other hospitals.

2.2. Participants

A total of 4636 VLBW infants born with a birth weight below 1501 g were registered in the database of the Premature Baby Foundation of Taiwan between 2007 and 2011. All 21 hospitals located across the island of Taiwan participated in the data collection. In addition to neonatal histories such as diagnoses, complications during hospitalization, and clinical outcomes from their health records at the time of discharge, the database also included antenatal and perinatal information. Data entry was conducted after death or discharge of infants from hospital. Patient information received by the database coordinator was cross checked with the national birth registry. Exclusion criteria included congenital anomalies and chromosome anomalies.

Gestational age was determined from maternal dates of the last menstrual period and the date of embryo transfer for *in vitro* fertilization. SGA infants were identified as having birth weights below the 10^{th} percentile for gestational age on sex-specific standards,[12] whereas AGA infants were defined as infants' birth weights between the 10^{th} and 90^{th} percentiles (inclusive) for gestational age. SGA—AGA match was carried out and SGA infants with two gestation age-matched AGA cases were selected in our study group. For each SGA case, two gestation age-matched AGA infants were randomly selected using the incidence density sampling approach in a 2:1 match.

2.3. Outcome variables

RDS was defined by clinical diagnosis as requiring surfactant therapy. The extent of intraventricular hemorrhage (IVH) and necrotizing enterocolitis (NEC) was graded according to the classification of Papile et al[13] and Bell et al,[14] respectively. Severe retinopathy of prematurity (ROP) was classified as Stage 3 to Stage 5 according to the international classification.[15] PVL was diagnosed by echolucent areas or persistent echogenicity in periventricular areas on coronal and sagittal views of cranial ultrasounds.[16] Bronchopulmonary dysplasia (BPD) was defined as infants requiring oxygen supplementation at the postconceptional age of 36 weeks.[17]

2.4. Statistical analysis

The Chi-square test and the Student *t* test were used to compare the distributions of categorical variables and continuous variables between two groups, respectively. For