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Incidence Trends and Risk Factor Variation in Severe Intraventricular Hemorrhage across a Population Based Cohort

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Objective To quantify the current burden of severe intraventricular hemorrhage (IVH), describe time trends in severe IVH, identify IVH-associated risk factors, and determine the contribution of mediating factors.

Study design The retrospective cohort included infants $22^{0/7}$-$31^{6/7}$ weeks of gestation without severe congenital anomalies, born at hospitals in the California Perinatal Quality Care Collaborative between 2005 and 2015. The primary study outcome was severe (grade III or IV) IVH.

Results Of 44 028 infants, 3371 (7.7%) had severe IVH. The incidence of severe IVH decreased significantly across California from 9.7% in 2005 to 5.9% in 2015. After stratification by gestational age, antenatal steroid exposure was the only factor associated with a decreased odds of severe IVH for all gestational age subgroups. Other factors, including delivery room intubation, were associated with an increased odds of severe IVH, though significance varied by gestational age. Factors analyzed in the mediation analysis accounted for 45.6% (95% CI 38.7%-71.8%) of the reduction in severe IVH, with increased antenatal steroid administration and decreased delivery room intubation mediating a significant proportion of this decrease, 19.4% (95% CI 13.9%-27.5%) and 27.3% (95% CI 20.3%-39.2%), respectively. The unaccounted proportion varied by gestational age.

Conclusions The incidence of severe IVH decreased across California, associated with changes in antenatal steroid exposure and delivery room intubation. Maternal, patient, and delivery room factors accounted for less than one-half of the decrease in severe IVH. Study of other factors, specifically neonatal intensive care unit and hospital-level factors, may provide new insights into policies to reduce severe IVH. *(J Pediatr 2018;■■:■■-■■).*

Severe intraventricular hemorrhage (IVH) is a significant source of morbidity for very low birth weight infants and is associated with adverse long-term outcomes.[1,2] The incidence of severe IVH reported by the National Institute of Child Health and Human Development Neonatal Research Network in 2012 was 13%.[3] Data from the Vermont Oxford Network reported a decrease in the median incidence of severe IVH from 9.4% (IQR 8.7%-10.2%) in 2005 to 7.9% (IQR 7.6%-8.2%) in 2014.[4] These data demonstrate the variable, but persistent burden of severe IVH for very low birth weight infants.

Many previous epidemiologic studies focused on the identification of IVH-associated risk factors to assess or calculate severe IVH risk, including gestational age, sex, antenatal steroid exposure, mode of delivery, and low Apgar scores.[5-7] However, aside from antenatal steroids, the relative impact and contribution of these factors in the development of IVH is not well described.[7] It is unknown whether changes in these factors help explain potential changes in the incidence of IVH over time and whether risk factors for IVH differ between infants of different gestational ages.

The goal of this study was to examine contemporary, population-based, generalizable data to characterize the changing landscape of severe IVH through describing the current burden of severe IVH, trends in severe IVH over time, and IVH-associated variables. We hypothesized that a detailed analysis of IVH-associated variables of infants at varying degrees of prematurity and a mediation analysis to quantify the contribution of relevant IVH-associated variables would provide new insights into risk factors for the development of severe IVH.

Methods

The California Perinatal Quality Care Collaborative (CPQCC) prospectively collects data from >90% of neonatal intensive care units (NICUs) in California, which at the time of this study reflected 127 NICUs. The CPQCC eligibility criteria include infants with a birth weight between 401 and 1500 g or a gestational age between $22^{0/7}$ and $29^{6/7}$ weeks. In addition, infants with a gestational age ≥30 weeks are included if the birth weight was <1500 g or if they met 1 of the following criteria:

CPQCC	California Perinatal Quality Care Collaborative
CPR	Cardiopulmonary resuscitation
IVH	Intraventricular hemorrhage
NICU	Neonatal intensive care unit

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noninvasive ventilation for >4 hours, intubation and ventilation for >4 hours, severe hyperbilirubinemia, early bacterial sepsis, surgery, acute transfer in or out of a NICU, and death.

The study cohort included infants born at $22^{0/7}$-$31^{6/7}$ gestational age weeks from January 2005 to December 2015. Gestational age was determined by the best available estimate in weeks and days. Where sources disagreed, obstetric measures based on last menstrual period or prenatal ultrasound took precedence over the neonatologist's estimate based on physical examination. Infants were assigned "year" based on their birth year. Prior to the application of exclusion criteria, there were 61 021 infants in the cohort. To minimize the incorrect estimation of gestational age, infants with a birth weight below the first percentile for gestational age or above the 99th percentile were excluded (n = 288). Additional exclusion criteria were infants with major congenital anomalies or anomalies of unknown severity (n = 4000), those who died in the delivery room (n = 2546), those without IVH imaging data (n = 3017), and those born in non-CPQCC associated NICUs (n = 7142). The final cohort included 44 028 infants.

Outcomes and Variables

Severe IVH was defined as any grade III or IV IVH documented in a CPQCC NICU by cranial imaging obtained prior to 28 days of life.[8] Information regarding the exact timing of imaging/diagnosis of IVH was not available. If bleeds of different severity were documented, the most severe grade was assigned to the patient and used for analysis. Infants with severe IVH were compared with those without severe IVH or with grade I or II IVH. Based on previous literature, variables of interest included birth weight, gestational age, birth weight small for gestational age, sex, multiple gestation, antenatal steroids, prenatal care, maternal hypertension, chorioamnionitis, maternal bleed, race/ethnicity, mode of delivery (cesarean or vaginal delivery), Apgar scores at 1 and 5 minutes, delivery room intubation, delivery room cardiopulmonary resuscitation (CPR), defined as the receipt of chest compressions and/or epinephrine), surfactant administration, death prior to hospital discharge, and birth year.[5,9-14] Data collection is performed by trained data abstractors based on definitions from the CPQCC, which uses standard definitions developed by the Vermont Oxford Network.[15,16]

Statistical Analyses

Analysis was completed using SAS v 9.4 (SAS, Cary, North Carolina) and Stata v 14.2 (StataCorp, College Station, Texas). The cohort was stratified into gestational age subgroups, 22-$23^{6/7}$, 24-$25^{6/7}$, 26-$27^{6/7}$, 28-$29^{6/7}$, and 30-$31^{6/7}$ gestational age weeks. Rates of severe IVH were calculated as crude and risk-adjusted rates that accounted for patient and hospital level factors. One-way ANOVA and Kruskal-Wallis tests were used to compare maternal and neonatal characteristics for infants with severe IVH to those without IVH or with grade I or II IVH. Multivariable logistic models were used to examine factors associated with severe IVH. Variables in the model included sex, birth weight, gestational age, multiple gestation, race/ethnicity, antenatal steroids, prenatal care, maternal hypertension, chorioamnionitis, mode of delivery, 1-minute Apgar score <3, 1-minute Apgar score <7, 5-minute Apgar score <3, 5-minute Apgar score <7, delivery room intubation, delivery room CPR, and surfactant administration with hospital applied as a random effect to adjust for clustering by site. Because of the collinearity of delivery room intubation and surfactant, only 1 variable, delivery room intubation, was kept in the final model. Infants, without cranial imaging, were unlikely to have IVH as they were bigger (mean birth weight 1242.9 g ± 528.1g) and older (mean gestational age 28.0 ± 3.2 weeks). There was no change in the frequency of missing IVH imaging data over the study period ($P = .91$). In addition, a sensitivity analysis was completed where infants without cranial imaging who survived to day of life 7 were included as infants without IVH.

A frequency analysis was performed to determine the incidence of severe IVH over time, stratified by gestational age. Linear regression models were used to determine if the change in the incidence of severe IVH was significant over time, as well as the rates of antenatal steroid exposure and delivery room intubation. A mediation analysis was performed to determine the proportion of the effect attributable to a variable or subset of variables in the change in the incidence of severe IVH over time. This was performed using serial multivariable generalized linear models and determining the change in the model coefficient for year ([base model coefficient-new model coefficient]/base model coefficient) with the addition of intermediary variables. This analysis produced an attributable percentage, which was the change in severe IVH incidence over time attributable to the new variables added to the model. The following sequential, additive models were run, with the specified variables added to the base model: (1) year and hospital, (2) sex, gestational age, and multiple gestation, (3) antenatal steroids, mode of delivery, and delivery room intubation were added individually, and then (4) all together. This analysis was also repeated with surfactant in place of delivery room intubation, and the results were unchanged. Given the interest in modifiable factors associated with severe IVH, the results associated with delivery room intubation are reported. The mediation analysis was performed for the whole cohort and then for each gestational age subgroup. To determine CIs for the attributable percentage in the mediation analysis, we performed a bootstrap analysis with 1000 iterations.

Results

During the study period, 44 028 infants met inclusion criteria. Of those, 24.2% (n = 10 640) had IVH, with 7269 (16.5%) developing grade I or II and 3371 (7.7%) developing grade III or IV. The rate of severe IVH was highest in the youngest subgroup, 22-$23^{6/7}$ gestational age weeks at 36.1% and decreased with increasing gestational age, 20.8% in 24-$25^{6/7}$, 9.5% in 26-$27^{6/7}$, 3.3% in 28-$29^{6/7}$, and 1.2% in 30-$31^{6/7}$. Cohort characteristics for those without IVH, with grade I or II IVH, and severe IVH were significantly different for the whole cohort (**Table I**; available at www.jpeds.com) and gestational age subgroups (**Table II**; available at www.jpeds.com). After multivariable analysis of the gestational age subgroups, significant,

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