Postnatal corticosteroids and risk of retinopathy of prematurity

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PURPOSE To investigate the association between postnatal steroids and retinopathy of prematurity (ROP) in neonates born with birth weights at the limit of viability (<500 g).

METHODS Data from the Pediatrix BabySteps Clinical Warehouse were retrospectively reviewed. The study population consisted of 1,472 neonates with birth weights of <500 g who were discharged alive from 167 NICUs between 1996 and 2013. Statistical significance for unadjusted comparisons between groups was determined using the χ^2 or t test. Logistic regression was used to calculate odds of ROP.

RESULTS In multivariate analysis, the odds of any ROP for steroid treated infants was 1.6 (95% CI, 1.2-2.2) compared to nontreated infants; the odds of advanced ROP was 1.7 (95% CI, 1.3-2.3).

CONCLUSIONS In our large study cohort of critically low birth weight infants ROP was more common in neonates exposed to postnatal steroids. (J AAPOS 2016;20:348-352)

Because of the beneficial effect of corticosteroids on lung function, especially in infants who are ventilator dependent, corticosteroids are frequently administered to very low birth weight (VLBW) neonates (birth weight <1500 g) to treat established or evolving lung disease.[1] However, over the last several years, there has been increasing concern that adverse neurodevelopmental effects may result from postnatal steroid use. A Cochrane Database System Review examined randomized controlled trials that had investigated the long-term outcome of preterm infants who had been treated with postnatal steroids within the first week of life: 12 trials reported an increase in adverse neurological effects including developmental delay, cerebral palsy, and abnormal neurological examination in the infants who had been treated with the postnatal steroids.[2] Because of the potential for adverse neurological effects, the American Academy of Pediatrics has advised that postnatal steroids be limited to certain clinical conditions.[3] However, the debate regarding the benefit of postnatal corticosteroid as a respiratory rescue therapy versus the potential harm of neurodevelopmental impairment in VLBW neonates continues.

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In addition to potential neurodevelopmental impairment from steroids, several observational studies of VLBW neonates have reported a significant association between postnatal steroid administration and an increased risk of retinopathy of prematurity (ROP).[1,4,5] However, many clinicians have been skeptical of these results because multivariate analyses cannot adjust for the marked clinical differences between VLBW neonates who receive steroids versus those who do not. This problem occurs because VLBW neonates represent a heterogeneous group of infants who range from those of very immature gestational age to those who are more mature but extremely growth retarded.[6] In addition, many substantive differences in risk factors for ROP exist in chronically ventilated neonates compared to premature infants without significant pulmonary disease.

The purpose of this study was to investigate the association between postnatal steroids and ROP risk by examining ROP risk in a large cohort of preterm neonates born at birth weights at the limit of viability (<500 g). This cohort represents a more homogeneous set of neonates because neonates at these critically low birth weights (and gestational ages) are at the highest vulnerability for a host of neonatal morbidities including ROP and bronchopulmonary dysplasia. Thus, clinical differences between steroid-treated and untreated neonates can be minimized.

We utilized data from Pediatrix BabyStep Clinical Data Warehouse, one of the world's largest repositories of neonatal data, to examine the incidence of ROP in a large cohort of preterm infants with birthweight of <500 g. This database includes information on >1,120,000 infants who had been cared for by Pediatrix Medical Group providers at US hospitals since 1996.[7,8] Data is automatically extracted from the daily medical record notes on each child admitted

by Pediatrix physicians At the current time, the Pediatrix Medical Group cares for nearly 25% of neonates in more than 300 NICUs across the U.S. The Pediatrix BabySteps Clinical Data Warehouse captures diagnostic and procedure coding data from the Pediatrix Medical Group electronic health record, which strictly adheres to the American Academy of Pediatrics Perinatal Section Coding Committee Guidelines.[7]

Methods

All data entry for the Pediatrix BabySteps Clinical Data Warehouse is verified on an ongoing basis by the Pediatrix Clinical Data Warehouse Information Technology team and by a database manager. The data from the Pediatrix BabySteps Clinical Data Warehouse is annually certified as deidentified and are compliant with the US Health Insurance Portability and Accountability Act of 1996. The data has been approved for use in research studies by the Western Institutional Review Board. In addition, an exemption for any additional institutional review board approval for use of the deidentified dataset in this study was granted by the Michigan State University Institutional Review Board.

The following 3 inclusion criteria were used for this study population were: (1) birth weight <500 g; (2) hospitalization survival (ie, discharged from hospital alive); (3) ophthalmic ROP examination results available.

The diagnosis and stage of ROP in the medical records was assigned by the board-certified ophthalmologists who performed the retinal ROP examinations. The retinal findings were standardized by classifying the examination results according to the International Classification of Retinopathy of Prematurity.[9-11] In most cases, multiple ROP examinations had been performed for each infant; the most advanced stage of ROP noted in the medical record was recorded as the infant's ROP stage. Although infants may have received additional ROP follow-up after hospital discharge, no post-discharge examination results were available for this study. Given that the average age at discharge was at a postmenstrual age close to term, however, it is highly probable that ROP severity would have reached its peak for the vast majority of the study participants before hospital discharge.

Study participants, born between 1996 and 2013, had been NICU inpatients at 167 different hospitals across the United States. Our study dataset included binary data (yes/no) on steroid exposure during pregnancy (ie, antenatal steroid) and after birth (postnatal steroid exposure). Steroid exposure included exposure to any type of steroids (betamethasone, dexamethasone, hydrocortisone, prednisolone, prednisone) for any indication. Also, the neonate may have been exposed to more than one type of steroid and for differing durations of treatment.

Statistical significance for unadjusted comparisons between groups was determined with Pearson's χ^2 test or t test (for parametric comparison of means) or Wilcoxon rank sum test (for nonparametric comparison of median Apgar scores). Multivariate models were adjusted for several covariates. To adjust for secular trends in steroid use over the years, different steroid practices in different hospitals and differences in ROP assessment by different ophthalmologists, year of birth, transfer status (born in NICU hospital or transferred in from another hospital), and NICU hospital facility were included as covariates. Because gestational age, birthweights and oxygen exposure/ventilation (number of days FiO_2 >0.21, days on high-flow nasal cannula, days on ventilation, and days on continuous positive airway pressure [CPAP]) are key risk factors for ROP, these were included as covariates. Comorbidities and other demographics that significantly differed between the steroid treated and untreated groups were included as covariates (patent ductus arteriosus, brain hemorrhage, necrotizing enterocolitis, bronchopulmonary dysplasia, sepsis, Apgar scores, and chronological age at hospital discharge). Antenatal steroid exposure and sex were also included as covariates.

Results

Data from 1,472 infant entries from the Pediatrix BabySteps Clinical Data Warehouse repository satisfied all three inclusion criteria and were used to compile the study dataset. Table 1 compares the characteristics of the postnatal steroid-treated and untreated neonates. Of the 1,472 infants, 1059 (71.9%) received postnatal corticosteroids and 413 (28%) did not. There were no significant differences between groups with regard to race, sex, or antenatal steroid exposure (ie, steroid exposure during fetal life). There were small but statistically significant differences between groups in mean birthweight, mean gestational age, and median Apgar scores. As expected, there were large, significant differences between groups in variables relating to oxygen exposure.

Table 2 provides the unadjusted incidence of ROP and other comorbidities of steroid-treated and nontreated neonates. The overall incidence of ROP (of any stage) for the entire cohort was 76.6% (1128/1472), and the overall incidence of advanced stage ROP (stages 3, 4, or 5) was 31.3%. The incidence of any ROP was significantly higher ($P < 0.0001$) in steroid-treated infants (80.5%) than in nontreated infants (66.8%); the incidence of advanced-stage ROP was also significantly higher ($P < 0.0001$) in the former (35.3%) compared to the latter group (21.1%). Steroid-treated infants also had a significantly higher incidence of bronchopulmonary dysplasia, sepsis, patent ductus arteriosus, and intracranial hemorrhage compared to nonsteroid treated neonates.

Table 3 provides the univariate and multivariate effect of postnatal steroid use and sepsis on the odds of ROP incidence for any ROP and for advanced ROP. All multivariate logistic regression included the covariates of postnatal steroids, bronchopulmonary dysplasia, and sepsis as well as the covariates of hospital facility, transfer status, antenatal steroid use, birth year, gestational age, birthweight, patent ductus arteriosus, Apgar scores, brain hemorrhage, discharge age, and sex as well as each type of O_2 exposure (number of days on FiO_2, artificial ventilation, high flow nasal cannula, and CPAP).

In multivariate analysis there was a 1.6 times greater odds (95% CI, 1.2-2.2) of any ROP for steroid-treated infants compared to nontreated infants and 1.7 times greater