Respiratory Support for Very Low Birth Weight Infants Receiving Dexamethasone

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Objective To assess how neonatal intensive care units followed the American Academy of Pediatrics guidelines for use of dexamethasone in preterm infants by evaluating respiratory support at the time of dexamethasone administration.

Study design This is an observational study of infants discharged from one of 290 neonatal intensive care units from 2003 to 2010. The cohort included very low birth weight (<1500 g birth weight) infants born at ≤32 weeks gestational age. The main outcome was respiratory support at time of exposure to dexamethasone. Significant respiratory support was defined as invasive respiratory support (conventional or high-frequency ventilation) with a fraction of inspired oxygen (FiO_2) > 0.3.

Results Of 81 292 infants; 7093 (9%) received dexamethasone. At the time that dexamethasone was initiated, 4604 (65%) of infants were on significant respiratory support.

Conclusions In accordance with the American Academy of Pediatrics recommendations, a majority of infants were on significant respiratory support when receiving dexamethasone, yet a substantial number of infants still received dexamethasone on less than significant respiratory support. Further research on reducing dexamethasone use in premature infants is required to decrease the risk of neurodevelopmental impairment. *(J Pediatr 2017;183:26-30).*

Bronchopulmonary dysplasia (BPD) is the most common pulmonary morbidity among premature infants, affecting approximately 22% of all very low birth weight infants (<1500 g birth weight).[1] BPD is associated with increased risk of mortality and morbidity among survivors, including chronic pulmonary disease, pulmonary hypertension, and long-term neurodevelopmental impairment.[2] In a large number of randomized controlled trials, dexamethasone decreased the incidence of BPD,[3-5] but its use was associated with increased risk of neurodevelopmental impairment and cerebral palsy.[4,6,7]

Based on these findings, in 2002 the American Academy of Pediatrics (AAP) and the Canadian Pediatric Society issued a joint policy statement advising against the use of dexamethasone for the prevention or treatment of BPD, and recommended limiting the use of dexamethasone to infants on "maximal ventilatory and oxygen support."[8] In this study, we sought to characterize the respiratory status of infants at the time of initiation of dexamethasone.

Methods

In this observational cohort study, we identified very low birth weight (<1500 g birth weight) infants, ≤32 weeks gestational age, admitted from 2003 to 2010 from 290 neonatal intensive care units managed by the Pediatrix Medical Group. We limited the analyses to infants born from 2003 to 2010 to capture clinical practices after the publication of the 2002 AAP guidelines regarding the use of dexamethasone[8] and before the new guidelines were published in 2010. The 2010 guidelines recommended against the use of high-dose dexamethasone but reported insufficient evidence to make any conclusions regarding the use of low-dose dexamethasone.[9] We identified infants who received a course of dexamethasone beginning in the first 120 postnatal days. We excluded any infants missing data describing respiratory support at the time of dexamethasone administration.

Data were obtained from a prospective electronic medical record generated by clinicians on all infants cared for by the Pediatrix Medical Group. Data on multiple aspects of care are entered into the system to produce admission notes, daily progress notes, procedure notes, and discharge summaries.[10] Information collected included demographics, medications (without dose), respiratory support,

AAP	American Academy of Pediatrics	HFV	High-frequency ventilator
BPD	Bronchopulmonary dysplasia	NC	Nasal cannula
CMV	Conventional mechanical ventilator	NCPAP	Nasal continuous peak airway pressure
FiO_2	Fraction of inspired oxygen		

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and diagnoses. This study was approved by the Duke University Institutional Review Board without the need for written informed consent as the data were collected without identifiers.

A course of dexamethasone was defined as >1 consecutive day of drug. Only the first course of dexamethasone was analyzed for each infant. Death was defined as death before hospital discharge. Respiratory support and fraction of inspired oxygen (FiO_2) were defined at the time of the start of the dexamethasone course as the significant respiratory support and FiO_2 observed on either the first day of dexamethasone or the preceding day. We considered both days to describe better the significant respiratory support leading to the clinician decisions to start dexamethasone.

We grouped infants into 4 categories based on respiratory support: (1) no support or oxygen supplementation via hood or tent; (2) nasal cannula (NC), high-flow nasal cannula, or nasal continuous positive airway pressure (NCPAP); (3) conventional mechanical ventilator (CMV); and (4) high-frequency ventilator (HFV). We also categorized infants by the FiO_2 required (≤0.3 or >0.3). We grouped infants based on postnatal day they received dexamethasone (<14 or ≥14 days of life), based on AAP guidelines identifying premature infants on the ventilator beyond 2 weeks of life as having a higher risk for BPD.[9] We defined "significant respiratory support" as CMV or HFV and $FiO_2 > 0.3$.

We defined BPD as continuous respiratory support (supplemental oxygen, NC, high-flow NC, NCPAP, CMV, or HFV) between 36 0/7 and 36 6/7 weeks, postmenstrual age. Room air challenge tests were not performed uniformly. Infants who were transferred, discharged, or died before this time were evaluated on their last day of hospitalization; if such an infant was on room air, the infant was defined as not having BPD, and if the infant was on respiratory support (including supplemental oxygen), then the BPD status was defined as "missing."

We calculated the risk of BPD or death using Neonatal Research Network BPD risk estimator (https://neonatal.rti.org/index.cfm?fuseaction=BPDCalculator.start).[11] This estimator uses gestational age, birth weight, sex, race or ethnicity, postnatal day, ventilator type, and FiO_2 to determine an infant's risk of mild, moderate, or severe BPD and death, as defined by the Neonatal Research Network. We estimated the risk of BPD or death based on the calculator's predictions for moderate BPD, severe BPD, or death. The estimator was only validated for infants with gestational age 23-30 weeks, birth weight 501-1249 g, and day of life ≤42, and any infants not meeting these criteria were removed from this particular analysis. The estimator assesses the risk of BPD on postnatal days 1, 3, 7, 14, 21, and 28. We rounded the day of starting dexamethasone to the nearest of these time points, until day of life 43—the day of life at which the estimator is no longer validated, so the calculated BPD risk was defined as "missing." Using the BPD estimator, infants with <50% chance of either death or severe or moderate BPD were defined as infants in which the potential risks of steroid administration outweighed the likely benefits.[12] To assess the efficacy of the BPD risk calculator, we compared predicted incidence of BPD or death with the actual incidence of BPD and death.

Finally, to assess the practices of each site in the Pediatrix Medical Group, we determined the proportion of infants from an individual site receiving dexamethasone on significant support. For this analysis alone, we excluded sites with <10 otherwise eligible infants, as these sites were presumed to have a low patient volume, which could bias the analyses.

Statistical Analyses

We used standard summary statistics (means, percentages, 5th and 95th percentiles) to describe the study variables. Infant-level continuous and categorical variables were compared using Student *t* test and χ^2 tests, respectively. We used a univariable logistic regression to calculate the ORs and examine the association between admission year and proportion of infants receiving mechanical ventilation upon starting dexamethasone. Infants who received dexamethasone but did not have respiratory data were assumed to be missing at random and excluded from the analysis. All analyses were conducted using Stata 13.1 (StataCorp, College Station, Texas) and assumed a significance level of $\alpha = 0.05$.

Results

During the study period, 81 292 very low birth weight infants were identified, and 7265 (9%) received dexamethasone (**Figure 1**; available at www.jpeds.com). Of these, 7093 (98%) from 181 sites had respiratory status data available, representing the cohort we analyzed (**Table I**). The first course of dexamethasone began on mean day of life 38 (5th, 95th percentile; 8, 87) with a mean duration of 6 days (2, 15). The first course of dexamethasone was administered after day of life 14 in 6170 (87% of total cohort) infants. At the time of dexamethasone initiation, 4604 (65%) infants were on significant respiratory support (CMV/HFV + > 0.3 FiO_2). Of the total cohort, 6064

Table I. Demographics and clinical characteristics of infants who received dexamethasone

Demographics and characteristics	n = 7093
Male	59%
Birth weight (g)	
<500	5%
500-749	45%
750-999	31%
1000-1499	19%
Gestational age (wk)	
≤24	29%
25-27	53
28-32	19%
Race/ethnicity	
White	46%
Black	31%
Hispanic	18%
Other	4%
Apgar score at 5 min	
0-3	8%
4-6	28%
7-10	64%
Died	11%
BPD	73%