Acute Responses to Diuretic Therapy in Extremely Low Gestational Age Newborns: Results from the Prematurity and Respiratory Outcomes Program Cohort Study

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Objective To determine if daily respiratory status improved more in extremely low gestational age (GA) premature infants after diuretic exposure compared with those not exposed in modern neonatal intensive care units.

Study design The Prematurity and Respiratory Outcomes Program (PROP) was a multicenter observational cohort study of 835 extremely premature infants, GAs of $23^{0/7}$-$28^{6/7}$ weeks, enrolled in the first week of life from 13 US tertiary neonatal intensive care units. We analyzed the PROP study daily medication and respiratory support records of infants ≤34 weeks postmenstrual age. We determined whether there was a temporal association between the administration of diuretics and an acute change in respiratory status in premature infants in the neonatal intensive care unit, using an ordered categorical ranking of respiratory status.

Results Infants in the diuretic exposed group of PROP were of lower mean GA and lower mean birth weight ($P < .0001$). Compared with infants unexposed to diuretics, the probability (adjusted for infant characteristics including GA, birth weight, sex, and respiratory status before receiving diuretics) that the exposed infants were on a higher level of respiratory support was significantly greater (OR, >1) for each day after the initial day of diuretic exposure.

Conclusions Our analysis did not support the ability of diuretics to substantially improve the extremely premature infant's respiratory status. Further study of both safety and efficacy of diuretics in this setting are warranted. *(J Pediatr 2018;■■:■■-■■).*

Trial Registration Clinicaltrials.gov: NCT01435187.

Premature neonates are at increased risk of respiratory distress syndrome (RDS) and chronic lung disease with respiratory insufficiency and failure owing primarily to lung immaturity and insufficient surfactant production. The sole approved treatment for RDS has been airway instillation of liquid surfactant. RDS and evolving chronic lung disease are marked by inflammation of the lung, and it has been hypothesized that this inflammation increases fluid infiltration into the lung parenchyma. Diuretics have been commonly used in neonatal intensive care units (NICUs) to treat these infants despite little evidence of efficacy. A recent work described the wide assortment of medications currently used in the NICU to treat and prevent long-term pulmonary complications.[1]

Diuretic prescribing patterns for premature infants receiving NICU care have been highly variable. Studies suggested short-term physiological benefit of diuretics with improved measures of lung compliance, airways resistance, and ventilator support.[2,3] However, there has been a paucity of information about acute responses to diuretics of extremely low gestational age (GA) newborns (ELGAN) and extremely low birth weight newborns managed in the modern NICU, with routine use of prenatal corticosteroids, postnatal surfactant, and advanced ventilatory support. Wide variations in practice suggested there was insufficient evidence to support guidelines for use of diuretics in premature infants.[4-7] For example, an analysis of the Pediatrix database indicated that approximately one-third of premature neonates received a diuretic at some point during their NICU stay.[5] These

BPD	Bronchopulmonary dysplasia
ELGAN	Extremely low gestational age newborn
ETT	Endotracheal tube
FiO_2	Fractional inspired oxygen
GA	Gestational age
NICU	Neonatal intensive care unit
PROP	Prematurity and Respiratory Outcomes Program
RDS	Respiratory distress syndrome

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variations in practice may be due in part to limited efficacy studies and confusion over the short-term vs long-term goals of therapy in this vulnerable population.

The National Heart, Lung, and Blood Institute supported the Prematurity and Respiratory Outcomes Program (PROP) and the *Eunice Kennedy Shriver* National Institute of Child Health and Human Development (National Institutes of Health) supported detailed medication data collection. PROP was an observational prospective cohort study of premature infants. The purpose of PROP was to identify mechanisms and associated functional and molecular biomarkers of respiratory disease risk of premature infants (available at: https://grants.nih.gov/grants/guide/rfa-files/RFA-HL-10-007.html). Details on the study design and standardized prospective data collection were reported previously.[8,9]

Given that many premature infants are exposed to diuretics, we sought to determine whether diuretics provided some benefit in tertiary NICU settings. The objective of this study was to determine if daily respiratory status improved more in extremely low GA premature infants after diuretic exposure compared with those not exposed.

Methods

We analyzed the daily medication and respiratory support records from a contemporary cohort of ELGAN infants in PROP. PROP investigators enrolled 835 infants in the first week of life with GAs of $23^{0/7}$-$28^{6/7}$ weeks at 13 tertiary US NICUs from August 2011 to November 2013.[8,9] Infants were excluded if viability was a concern, if the infant had a significant birth defect, or if the family was unlikely to be available for follow-up to the primary 1-year outcome. A National Heart, Lung, and Blood Institute Observational and Safety Monitoring Board provided human subjects oversight, in addition to institutional review boards for each participating site. At least 1 parent or guardian provided informed consent for each child participant. The study was registered on clinicaltrials.gov (NCT01435187).

Daily data included respiratory medications and respiratory support measures administered by NICU clinicians according to their usual care practices. Respiratory medications included inhaled bronchodilators, inhaled corticosteroids, systemic corticosteroids, methylxanthines, pulmonary vasodilators, and diuretics. Diuretics recorded were furosemide, bumetanide, chlorothiazide, hydrochlorothiazide, and spironolactone.[10] Respiratory support measures recorded included invasive ventilation with an endotracheal tube (ETT), noninvasive support without an ETT, and nasal cannula. Level of flow and fractional inspired oxygen (FiO_2) were also recorded.

Statistical Analyses

We asked if there was a temporal association between the administration of diuretics and an acute change in respiratory status in premature infants in the NICU. Respiratory status was ranked categorically as (1) room air only, (2) nasal cannula with <2 lpm flow, (3) noninvasive mechanical ventilation or nasal cannula with ≥2 lpm flow, (4) invasive mechanical ventilation with ETT, and (5) deceased. Daily respiratory status was recorded for each baby from birth at ≤34 weeks postmenstrual age. Observations were censored at 34 weeks, because transfer/discharge of PROP infants occurred as early as this time. Diuretic exposure was categorized in the model as unexposed, consecutive exposure days 1-7, consecutive exposure day >7, a 1-day course, and 3-day washout period. A separate model term was used for 1-day courses of diuretics, owing to uncertainty about the indication for use (eg, prevention of blood transfusion-induced fluid overload). The 3-day washout period model term was used to capture washout effects. We used a generalized linear model of the outcome fit via generalized estimating equations to account for correlation among observations from the same baby. The model gave predicted odds under a proportional odds assumption of a worse outcome (in the direction of outcome 5, deceased) for those in each exposed group (consecutive days 1-7, consecutive day >7) compared with unexposed days, adjusting for infant birth weight, infant GA at birth, infant race, infant sex, site, and multiplicity of birth. The baby's current age (days) was included in the model as a linear term. To account for the current status and trajectory of outcome at the time of exposure, the baby's outcome on the previous day (day 0; included as categorical term), the change of outcome from day -2 to day 0 (included as linear term), and the change of outcome from day -1 to day 0 (included as linear term) were also included in the model. Current exposure to caffeine, any bronchodilator drugs, any inhaled corticosteroids, or any systemic corticosteroids were also adjusted for by separate terms in the model. SAS (version 9.3; SAS Institute, Cary, North Carolina) procedure GENMOD was used to analyze the data.

We also analyzed a matched cohort to confirm our findings. The matched cohort was selected as follows: (1) All babies were aligned by postnatal day. (2) Babies became eligible for the exposed cohort on the second consecutive day of diuretic use. (3) When a potential participant became eligible for the exposed cohort, we looked for unexposed babies who matched the exposed baby in 4 categories (5-level respiratory support status on cohort day 1, 5-level respiratory support status on cohort day 0, completed GA in weeks, and sex). (4) One baby was selected at random from eligible matched babies to be entered into the unexposed cohort. (5) Finally, we continued until no more matches were found, yielding 245 match pairs of babies, each with 1 exposed and 1 unexposed baby. The matched cohorts were compared by the Sign test to see if the difference in respiratory support status on cohort days 1 and 2 for the pairs (exposed–unexposed) had positive median and hence a higher level of respiratory support.

Results

Among 835 infants enrolled in PROP,[8] 483 were exposed at least once to a diuretic and 352 were never exposed (unexposed). There were 3 babies without any medication information that did not enter the statistical model or impact the

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