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Prolonged furosemide exposure and risk of abnormal newborn hearing screen in premature infants

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ABSTRACT

Background: At very high doses, furosemide is linked to ototoxicity in adults, but little is known about the risk of hearing loss in premature infants exposed to furosemide.
Aims: Evaluate the association between prolonged furosemide exposure and abnormal hearing screening in premature infants.
Study design: Using propensity scoring, infants with prolonged (≥28 days) exposure to furosemide were matched to infants never exposed. The matched sample was used to estimate the impact of prolonged furosemide exposure on the probability of an abnormal hearing screen prior to hospital discharge.
Subjects: A cohort of infants 501–1250 g birth weight and 23–29 weeks gestational age discharged home from 210 neonatal intensive care units in the United States (2004–2013).
Outcome measures: We defined abnormal hearing screen as a result of either "fail" or "refer" for either ear.
Results: Altogether, 1020 infants exposed to furosemide for ≥28 days were matched to 790 unique infants never exposed, yielding a total of 1042 matches due to sampling with replacement and propensity score ties. Matching resulted in a population similar in baseline characteristics. After adjusting for covariates, the proportion of infants with an abnormal hearing screen in the furosemide-exposed group was not significantly higher than the never-exposed group (absolute difference 3.0% [95% CI −0.2–6.2%], P = 0.07).
Conclusions: Prolonged furosemide exposure was associated with a positive, but not statistically significant, difference in abnormal hearing screening in premature infants. Additional studies with post-hospital discharge audiology follow-up are needed to further evaluate the safety of furosemide in this population.

1. Introduction

Bronchopulmonary dysplasia (BPD) is one of the most common complications associated with preterm birth and is the leading cause of pulmonary morbidity in premature infants [1]. Additionally, BPD can lead to long-term growth and neurodevelopmental impairment [2]. Early pulmonary edema and excessive administration of fluid are associated with increased risk of developing BPD [3,4]. Therefore, diuretics are frequently prescribed off-label to premature infants hospitalized in neonatal intensive care units (NICUs) to reduce excess fluid in the lungs, thereby promoting gas exchange and decreasing the need for respiratory support [5]. Approximately 40% of premature infants are exposed to at least 1 diuretic while in the NICU [6]. Furosemide is the most widely used diuretic in premature infants < 1500 g birth weight with evolving BPD for both short-term and prolonged therapy [7].

Abbreviations: BPD, bronchopulmonary dysplasia; FiO_2, fraction of inspired oxygen; GA, gestational age; NICU, neonatal intensive care unit

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In adult populations, administration of furosemide at high doses is associated with ototoxicity [8,9]. Little is known about ototoxicity associated with furosemide administration in infants. Case control studies in small cohorts of premature infants have suggested an association between furosemide and an increased risk for sensorineural hearing loss [10,11]. However, more recent studies have suggested that severity of illness rather than furosemide exposure is associated with an increased risk of hearing loss in premature infants [12,13]. Despite the frequent prolonged use of furosemide in premature infants in the United States, the risk of hearing loss associated with exposure to furosemide for prolonged periods is uncertain. We sought to evaluate the association of prolonged furosemide exposure and abnormal hearing screening in this population.

2. Methods

2.1. Study design and setting

We identified infants discharged home from 210 United States NICUs managed by the Pediatrix Medical Group between 2004 and 2013. Data are extracted from admission notes, daily progress notes, and discharge summaries; data contain information about diagnoses, procedures, diagnostic tests (including laboratory evaluations), and medications received. After extraction, data are transferred to a data warehouse for quality improvement and research initiatives [14]. We included infants 501–1250 g birth weight and 23–29 weeks gestational age (GA) at birth. We excluded infants who died during hospitalization, were transferred to another institution, did not have hearing screen results, or were missing data that were needed to estimate BPD risk at postnatal day 7 (including race or ethnicity, fraction of inspired oxygen [FiO_2], and ventilator status). We also excluded infants exposed to furosemide for < 28 days because our goal was to study the impact of prolonged exposure to furosemide. We chose a cut-off of 36 weeks postmenstrual age because that is the age at which BPD is diagnosed using many common clinical definitions [15], and we were interested in examining the safety of furosemide when used for the prevention of BPD. We collected demographics, medication data, respiratory support information, and hearing screen results. We also collected data on risk factors for hearing loss, including cytomegalovirus infection, vancomycin exposure, gentamicin exposure, and serum bilirubin levels. This study was approved by the Duke University Institutional Review Board with a waiver of informed consent.

2.2. Outcomes and definitions

We referred to the day of birth as postnatal day 0. We defined abnormal hearing screen as a result of either “fail” or “refer” for either ear. Either otoacoustic emission or brainstem auditory evoked response was used to evaluate hearing in the infants. If multiple hearing screens were performed, then the result of the final recorded screen was included in the analysis. If multiple hearing screens were performed on the date of the final hearing screen with conflicting results, then the infant's best result on that date was recorded. Meningitis was defined as a cerebrospinal fluid culture positive for bacteria not generally considered contaminants, including probable and definite coagulase-negative *Staphylococcus* [16].

2.3. Statistical analysis

We compared the prevalence of abnormal hearing screens between infants who had received ≥28 days of furosemide prior to 36 weeks postmenstrual age and infants who had never been exposed to furosemide. Because exposure to furosemide is likely to be associated with severity of illness, we hypothesized that the treated and untreated groups would be very different from one another. Therefore, we used propensity score matching on observable characteristics to construct a sample of untreated infants who were similar to treated infants. We included the following variables in a logistic regression model to generate propensity scores: GA group, small for GA status, sex, race, ventilator status on postnatal day 7, maximum FiO_2 on postnatal day 7, prenatal steroid exposure, and risk of severe BPD or death on postnatal day 7 using a model developed by the National Institute of Child Health and Human Development Neonatal Research Network [17,18]. We also included cytomegalovirus diagnosis, maximum bilirubin level > 15 mg/dL, exposure to gentamicin, exposure to vancomycin, meningitis, and intraventricular hemorrhage grade III or IV, because these have been suggested as risk factors for hearing loss [19–23]. Non-linear effects were expected for GA and FiO_2, so we included quadratic interaction terms for these covariates. We also included an interaction term between FiO_2 and ventilator status to improve covariate balance between treated and control groups. The Neonatal Research Network model included GA, birth weight, ventilator status on postnatal day 7, maximum FiO_2 on postnatal day 7, antenatal steroid exposure, male sex, and race. We matched infants and controls using nearest-neighbor matching based on their estimated propensity scores [24]. To obtain valid standard errors of the effect of furosemide exposure and to minimize bias, we sampled with replacement from the population of unexposed infants [25]. When there were multiple unexposed infants with equal propensity scores nearest to an exposed infant, we included all of these unexposed infants as controls and used frequency weighting to account for multiple matches per exposed infant.

We examined the distributions of propensity scores across the groups using histograms and kernel density plots. We evaluated the balance of covariates between the groups by comparing the matched standardized differences in means and variances between the 2 groups. Samples were considered well-matched if the standardized difference in means was < 0.1 for each covariate and the kernel density plots revealed no apparent anomalies. We then used the matched sample to estimate the average effect of furosemide exposure on abnormal hearing screen. All statistical analyses were performed using STATA v. 15.1 (StataCorp LP, College Station, TX).

3. Results

We identified 1020 infants exposed to furosemide for ≥28 days and 12,900 infants never exposed to furosemide who met criteria for the study (Fig. 1). The median age at which furosemide was started was 12 days (25th, 75th percentiles: 7, 19), and the median duration of furosemide exposure was 40 days (33, 50). Most infants were prescribed either 1 course (313/1020; 31%) or 2 courses (260/1020; 25%) of furosemide.

The 1020 infants exposed to furosemide for ≥28 days were matched to infants without furosemide exposure. Because some exposed infants had > 1 matching control with identical propensity scores, there were a total of 1042 matches, which were reweighted to yield 1020 controls. Some control infants were matched to > 1 infant in the exposed group, so the control group consisted of 790 unique infants. Propensity score matching resulted in a population that was similar in baseline characteristics (Table 1). The median (interquartile range) of GA, birth weight, and risk of moderate or severe BPD or death at postnatal day 7 in the furosemide exposed group were 25 weeks (24–27), 770 g (660–910), and 70% (55–82%) compared with 26 weeks (25–27), 790 g (690–945), and 66% (48–79%) in the never-exposed group. In the furosemide-exposed group, 140/1020 infants (14%) failed the newborn hearing screen compared with 82/790 infants (10%) in the never-exposed group.

Risk factors known to be associated with hearing loss, including cytomegalovirus infection, exposure to vancomycin, and elevated serum bilirubin level, were slightly more prevalent in the furosemide-exposed group compared with the never-exposed group (Table 1). Cytomegalovirus infection and elevated bilirubin levels ≥15 mg/dL were uncommon in both groups. Almost all infants in the exposed and