Lung Ultrasound Assessment of Pulmonary Edema in Neonates with Chronic Lung Disease Before and After Diuretic Therapy

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Abstract

Introduction: Bronchopulmonary dysplasia (BPD) is characterized by lung injury with varying degrees of disrupted alveolarization, vascular remodeling, inflammatory cell proliferation, and pulmonary edema. Diuretics are often used to ameliorate the symptoms or progression of BPD. Our primary objective was to use lung ultrasound (LUS) to determine if diuretics decrease pulmonary edema in infants with BPD. The secondary objective was to assess changes in respiratory support during the first week after initiation of diuretics. **Methods:** Premature infants requiring non-invasive respiratory support and starting diuretic therapy for evolving BPD were compared with a similar group of infants not receiving diuretics (control). For the diuretic group, LUS exams were performed before and on days 1, 3 and 6 after initiation of treatment. For the control group, LUS was performed at equivalent time points. A composite pulmonary edema severity (PES) score of 0 to 5 was calculated based on the total number of B-lines in 6 scanned areas. Respiratory support parameters (FiO2, nasal cannula flow or CPAP) were also recorded. **Results**: Infants in the diuretic (n=28) and control (n=23) groups were recruited at median corrected gestational ages of 34.2 (33.3-35.9) and 34.0 (33.4-36.3) weeks, respectively (p=0.82). PES scores, FiO2, and respiratory flow support decreased significantly from day 0 to 6 (p<.0001, p=0.001, and *p=0.01,* respectively) in the diuretic group, but not in the control group. **Conclusion:** Diuretic use is associated with decreased pulmonary edema and improved oxygenation in infants with BPD during the first week of treatment.

INTRODUCTION

Bronchopulmonary dysplasia (BPD) or neonatal chronic lung disease (CLD) represents a common and complex cardiorespiratory morbidity that affects preterm infants. Despite advances in care, the prevalence of BPD has remained constant due to increased survival of extremely low gestational age newborns (ELGAN).[1] It is estimated that 45% of ELGANs are diagnosed with BPD. Pathologically, BPD is characterized by abnormal lung development and lung injury with varying degrees of disrupted alveolarization, vascular remodeling, inflammatory cell proliferation and pulmonary edema. Lung morbidity associated with BPD increases the risks for prolonged oxygen and respiratory support requirements, pulmonary hypertension, impaired growth, and poor neurodevelopmental outcomes. As such, the prevalence of BPD represents an essential indicator for benchmarking the quality of neonatal care.[2]

Management of BPD includes strategies to avoid invasive mechanical ventilation together with aggressive pharmacologic and nutritional interventions. While limiting mechanical ventilation and enhancing caloric intake have been shown to improve outcomes in BPD patients, the long-term benefits of medications such as steroids and diuretics for BPD remain uncertain. In ELGANs with BPD who require increased intravenous or enteral intake to ensure metabolic requirements, diuretics are used very commonly to improve pulmonary function despite limited data regarding their-long term efficacy and safety.[3-5] In the short term,

they improve pulmonary function by decreasing interstitial pulmonary fluid, which can contribute to increased lung compliance, decreased airway resistance, and subsequently decreased respiratory support.[6-10] Despite these improvements in pulmonary mechanics, a series of 2011 Cochrane reviews did not demonstrate long-term benefits, so routine diuretic use for infants with active or developing chronic lung disease was not recommended.[11,12] In contrast, a more recent retrospective study of over 37,000 premature infants, approximately half of whom had received furosemide, found that for every 10% increase in furosemide exposure-days, there was a 4.6% decrease in the incidence of BPD.[3]

Recent advances in lung ultrasound (LUS) diagnosis of neonatal diseases offer more sensitive detection of pulmonary edema regardless of its cause.[13] Excess water outside of pulmonary blood vessels can be quantified using LUS by the finding of "B-lines". In animal studies, the number of B-lines has been directly correlated with the severity of pulmonary edema.[14] Studies in neonates with congenital heart disease with pulmonary overflow have found LUS to be a useful tool to assess pulmonary edema.[15] Similar findings have been reported in infants with pulmonary edema caused by patent ductus arteriosus.[16]

Our primary objective was to quantify and compare pulmonary edema before and after initiation of diuretic therapy for infants with evolving CLD using LUS. The secondary objective was to assess changes in respiratory support parameters during the week after initiation of diuretics.

METHODS

We prospectively studied infants with evolving CLD treated with oxygen and non-invasive respiratory support from February 2020 to December 2021. The study was approved by Northwell Health Institutional Review Board (Manhasset, NY). Informed consent was obtained from parents before enrollment.

Study design

Infants born at 24-30 weeks of gestation treated with oxygen via either CPAP or nasal cannula (NC) for evolving CLD *and* history of at least one of the following: failed respiratory support weaning, chest X-ray characteristic of pulmonary edema, and/or increased work of breathing (tachypnea, intercostal retractions) were recruited. Infants with major congenital anomalies, lung anomalies, pulmonary hypertension, or cardiac anomalies (including ASD, VSD, and PDA) were excluded from the study. Infants in the diuretic group were started on diuretic therapy at the discretion of their physicians and compared with the control group of infants not receiving diuretics. Oral diuretic regimens included: furosemide only, furosemide followed by hydrochlorothiazide in those that responded to initial furosemide trial, hydrochlorothiazide and spironolactone, and hydrochlorothiazide only. In the diuretic group, LUS exams were performed within 1 day prior to the start of diuretic treatment (day 0), and on days 1, 3 and 6 after the first dose of diuretic. In the control group, LUS exams were performed at the same time points.

Ultrasound exams

For each LUS exam, 3 areas of the lung on each side, each including at least 4 ribs and 3 intercostal spaces, were scanned for B-lines: anterior, lateral and posterior (Figure 1). A 10-second video of each area was recorded and scored. A composite Pulmonary Edema Severity (PES) score of 0 to 5 was then calculated based on the total number of B-lines (0 = 0-5 B-lines, 1 = 6-10 B-lines, 2 = 11-15 B-lines, 3 = 16-20 B-lines, 4 = <3 coalescent B-lines, >3 coalescent B-lines). Ultrasound exams were performed with the Zonare Z.One Pro machine using a 14 MHz linear transducer (Mindray, Shenzhen, China). Ultrasound gel was prewarmed and the transducer disinfected before and after each evaluation. During the exam, infants were consoled with a pacifier. If an infant had oxygen desaturation below 80% or bradycardia below 80 bpm, the exam was interrupted to allow the infant to recover. No sedation was used during the LUS exams.

Respiratory support parameters

FiO2 and amount of nasal cannula (NC) flow or CPAP required were recorded on days 0, 1, 3, and 6. A decrease in NC flow of at least 0.5 L/min, decrease in CPAP pressure of at least 1 mm Hg, or change from CPAP to NC were considered a significant wean.

Statistical analysis

Study data are retained in a Northwell Health RedCap database. Statistical analysis was carried out using SAS version 9.4 software (Cary, NC). Continuous variables were reported as medians and interquartile ranges. Categorical variables were reported as frequencies and percentages. Wilcoxon rank sum tests were used to test differences in the distribution of continuous variables. Chi-square test and Fisher exact test were used for the comparison of proportions of categorical variables. Wilcoxon rank sum tests were used to test the differences in PES and FiO2. Significant weaning of respiratory support was examined as a dichotomous variable and Chi-square test was used to test differences between the study and control groups. P -values of <0.05 were considered statistically significant. We used two coefficients for the analysis of both interrater and intrarater agreement: Gwet's AC2 and Brennan-Prediger's Kappa.

RESULTS

Fifty-one infants were enrolled, 28 in the diuretic group and 23 in the control group. The groups were similar for gestational age, post-conceptional age at enrollment, use of caffeine and prenatal steroids and gender, and had similar incidences of chorioamnionitis, small for gestational age birth weight, and patent ductus arteriosus (Table 1). Mean corrected gestational age when diuretics were started was 34.2 (33.3-35.9) weeks in the diuretic group and 34.0 (33.4-36.3) in the control group. We performed 306 LUS scans. An aggregate of 51 minutes of recorded LUS video clips was analyzed by neonatology fellows trained in LUS (GK, FF) and a neonatology attending experienced in LUS (DK). Interobserver (GK, DK) and intraobserver (DK) variability scores were obtained. Interobserver Gwet's AC2 and Brennan-Prediger Kappa coefficients were 0.98 and 0.98 respectively. Intraobserver Gwet's AC2 and Brennan-Prediger Kappa coefficients were 0.97 and 0.97 respectively. These scores indicate very high levels of agreement.

PES scores and FiO2 decreased significantly from day 0 to 6 (p <.0001 and p =0.001, respectively) in the study group, but not in the control group (Figures 2 and 3). PES was significantly different between the groups on both day 3 (p =0.02) and on day 6 (p =0.001). FiO2 was significantly different between the groups on day 3 (p =0.017) but not on day 6 (p =0.52). Compared to the control group, the diuretic group had significantly greater wean of the respiratory flow support from day 0 to day 6 (*p=0.01*) (Figure 4).

DISCUSSION

The use of LUS in studying respiratory function of preterm infants has been well established. It has been used to predict the need for surfactant administration and/or respiratory support.[17-20] Using LUS to diagnose neonates with pulmonary edema has been shown to be more sensitive and with greater negative predictive value than X-rays.[21] Similarly, LUS showed good positive predictive value in the assessment of the early risk for BPD in ELGANs.[22] Surprisingly, despite the controversy, LUS has not been systematically used in the evaluation of diuretic effect in premature infants diagnosed with BPD. Recently, a very small study used LUS to evaluate a heterogeneous group (4/18 neonates had PDA) of preterm neonates with pulmonary edema treated with diuretics. The study showed lower LUS scores in the group of diuretic responders compared to non-responders. However, this pilot study enrolled neonates quite early in life, with diuretics being administered at a mean of 31 days of life. The study concluded that responders were treated with diuretics for much shorter periods and ultimately developed less severe BPD.[23]

We found that diuretic therapy was associated with significant decrease in pulmonary edema, FiO2 requirement, and respiratory flow support compared to the control group by day 3. FiO2 requirements were not different between the diuretic and control groups on day 6, either because they were both low and approaching the room air target on day 6, or because clinicians preferentially weaned respiratory flow support before FiO2 in the diuretic group. It is also possible that infants developed tolerance to diuretics after prolonged use.[24,25] In the diuretic group, 46% of infants were treated with diuretics for a duration of 7-10 days, and 3.6% of them had a rebound increase in need for FiO2 or respiratory flow support upon cessation of diuretic therapy. Our findings are consistent with previous studies showing that diuretics can improve O2 requirements and respiratory mechanics in infants.[26] Although, there is only limited previous data on the use of pulmonary edema scores in neonates, the correlation of decreasing scores with decreasing respiratory support

parameters in our subjects supports their validity.

A recent retrospective longitudinal cohort study confirmed the long-established association between chronic diuretic use and electrolyte disturbances requiring electrolyte supplementation, especially in infants treated with thiazides.[27] In our study group, 25% of infants had to be supplemented with either NaCl and/or KCl. This common side effect together with other concerns related to diuretic use such as ototoxicity, metabolic bone disease, and nephrocalcinosis underline the importance of careful evaluation of the need for diuretics in infants with CLD.

Our study has several limitations. The specific indications for diuretics in BPD are unclear, and thresholds for treatment were heterogeneous in our cohort, based on clinical experience and preference. In addition, infants in the diuretic group received several distinct regimens based on clinician preference, and the study was not adequately powered to compare them. It is also important to note that, while diuretics have short-term beneficial effects on respiratory function, they have not been associated with a decrease in long-term outcomes or length of hospital stay.[28] We could not evaluate the length of the hospital stay in our study because several infants from the control group eventually were later treated with diuretics.

CONCLUSIONS

Diuretics decrease lung edema and improve oxygenation in infants with BPD. Further study and refinement of LUS techniques in evaluation of pulmonary status and response to therapies may help optimizing the care of infants with BPD. In addition, well-controlled, prospective studies must further delineate risk-benefit ratios associated with the use of different diuretic therapies.

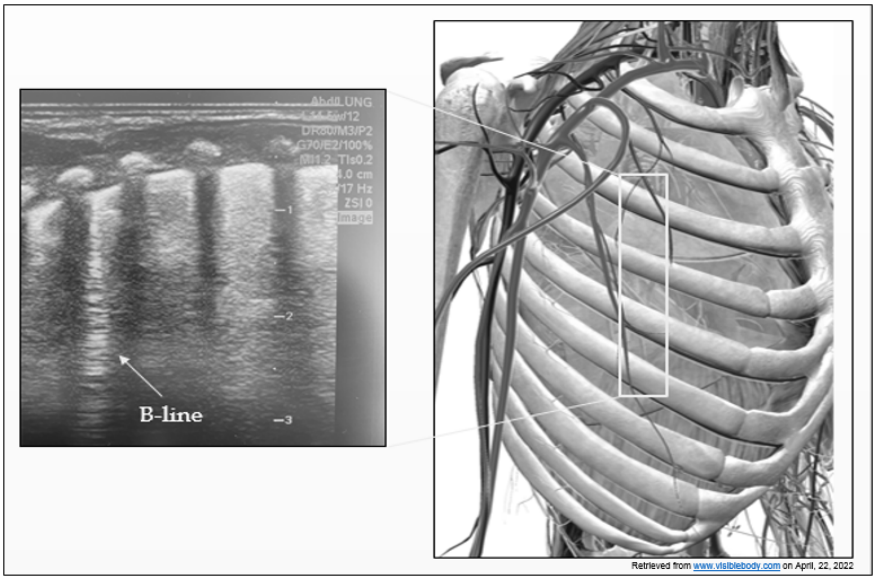

Figure 1: Lung ultrasound.

Infant characteristics	**Diuretic group (N=28)**	**Control group (N=23)**	***p*-value**
Gestational age, weeks[a]	26.6 (26.0-28.3)	27.30 (25.6-28.1)	0.82
Birth weight, grams[a]	1018.5 (676.5-1192.5)	860 (655.0-1110.0)	0.35
Prenatal steroids	21 (75.0 %)	21 (82.61 %)	0.73
Chorioamnionitis	5 (17.8 %)	6 (26.1 %)	0.51
Male	13 (46.4 %)	14 (60.9 %)	0.30
Small for gestational age	7 (25.0 %)	6 (26.1 %)	0.93

Infant characteristics	Diuretic group (N=28)	Control group (N=23)	p-value
History of caffeine use	26 (92.8 %)	23 (100.0 %)	0.24
History of PDA treatment	10 (35.7 %)	9 (39.3 %)	0.80
Gestational age at enrollment, weeks[a]	34.2 (33.3-35.9)	34.0 (33.4-36.3)	0.82

[a]median, IQR

Table 1: Diuretic and control group demographics.

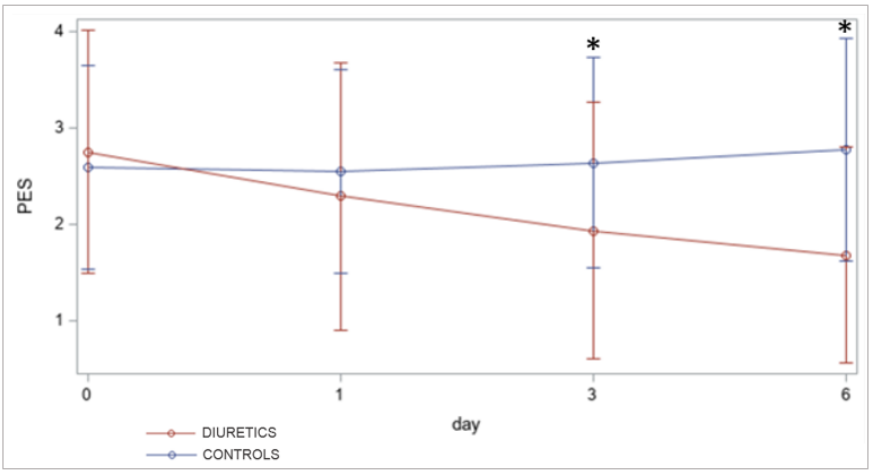

Figure 2: Pulmonary edema severity score (PES) from day 0 to day 6.

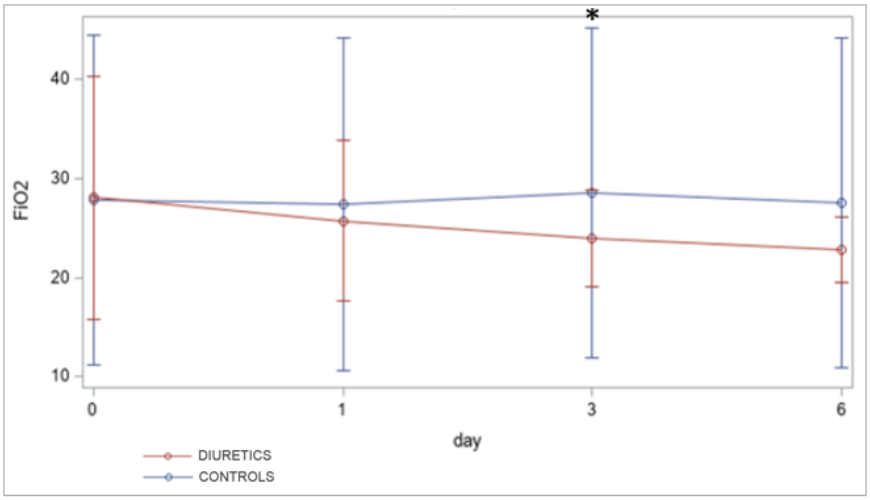

Figure 3: FiO2 requirement from day 0 to day 6.

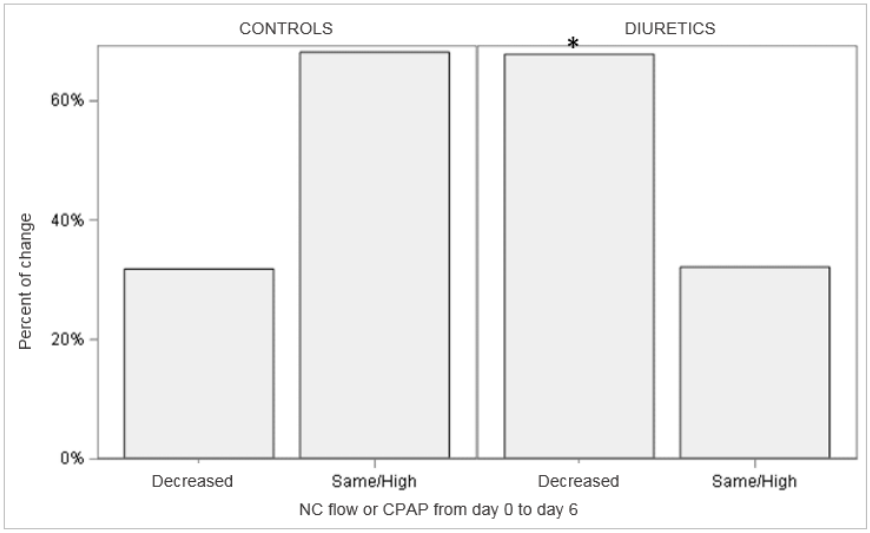

Figure 4: Respiratory flow support from day 0 to day 6.

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CONFLICTS OF INTEREST

The authors declare no conflicts of interest.

AUTHOR CONTRIBUTIONS

Kasniya Gangajal - US scanning (lead), writing original draft (co-lead), conceptualization (co-lead),

Barry Weinberger - original draft review and editing (equal)

Jane Cerise - data analysis (lead)

Margaret Pulju - original draft review and editing (equal),

Vitaliya Boyar - original draft review and editing (equal), study supervision (lead) Florin Frunza - US scanning (supporting)

Dalibor Kurepa - conceptualization (lead), US scanning (supporting), writing original draft (lead).

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available in RedCap data base.