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Use of Diuretics for Bronchopulmonary Dysplasia Increases Metabolic Bone Disease in Preterm Infants

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Abstract

Objective: Preterm infants (PI) are at increased risk of developing metabolic bone disease (MBD).This study assessed the association of diuretics for bronchopulmonary dysplasia (BPD) with MBD.

Study Design: This retrospective study included infants ≤30 weeks gestation and birth weight ≤1500 grams. Infants were divided into diuretic group and control group. Diuretic use was defined as hydrochlorothiazide and spironolactone for >7 days and MBD as PTH >100 mg/dL. Data was analyzed using SPSS and p <0.05 was considered significant.

Results: The study included 201 infants, with a mean gestational age 26.31 ± 1.73 weeks. There were 68 (33%) in the diuretic group vs. 133 (67%) in the control group. 41 vs. 24% ($p<0.05$) infants in the diuretics group who received diuretics for BPD also developed MBD. 80% vs. 20% ($p<0.001$) infants with BPD were treated with diuretics. Diuretics did not improve the respiratory status in these PI. We found infants given diuretics remained on ventilation for longer total number of days ($p<0.001$).

Conclusion: PI treated with diuretics for BPD are more likely to develop MBD without any significant improvement in respiratory status.

Abbreviations

BPD (bronchopulmonary dysplasia); MBD (metabolic bone disease); PI (premature infants); PTH (parathyroid hormone)

Introduction

Bronchopulmonary dysplasia (BPD) is a chronic lung disease that develops because of neonatal/perinatal lung injury. It is the most common respiratory complication of prematurity and is associated with an increased risk of death and poor neurodevelopment outcomes [1]. Currently, there is no US Food and Drug Administration-approved treatment to prevent BPD. Many off-label therapies such as caffeine (timing and duration still under investigation), vitamin A, postnatal systemic steroids (associated with poor long-term neurodevelopment outcomes), and diuretics are used in infants with BPD (no proven efficacy and safety profile) [2].

Long-term use of diuretics in infants with BPD is common to improve lung mechanics and gas exchange. The rationale for this practice lies in targeting clinical, radiographic, and pathologic evidence of interstitial and peribronchiolar pulmonary edema [3] and some studies show that occasionally diuretics improve gas exchange by improving lung compliance and decreasing pulmonary resistance [4]. Hydrochlorothiazide and spironolactone combination is the most used diuretic combination in infants with BPD [5-8] Thiazides and spironolactone both act on the distal tubule, and their combined use causes fever electrolyte abnormalities compared to loop diuretics such as furosemide.

Prematurity also predisposes neonates from the time of birth, towards developing metabolic bone disease (MBD). Approximately 80% of fetal bone mineralization occurs in the third trimester of pregnancy (32-36 weeks) [8]. This mineralization and accretion is often lost when a neonate is born prematurely. Studies have shown that although MBD may be a self-limiting condition, its long-term effect on stature, bone development, kidney function and future risk of osteoporosis is not to be dismissed [9,10]. Orth et al attempted to study the effect of early versus late initiation of diuretics in patients with MBD and found no difference in the development of MBD based on the timing of exposure [11]. In another study by Chen et al, prolonged use of diuretics > 2 weeks was noted to be a risk factor for the development of MBD in neonates ≤ 32 weeks gestation [12]. The role of chronic diuretic use for BPD and the increased risk of developing MBD in premature infants (PI) remain undetermined. The aim of this study was to determine the association of chronic diuretic use for BPD and MBD in PI.

Methodology

Study Population: This is a retrospective case-control study conducted at level IV neonatal intensive care unit at The University of Texas Medical Branch (UTMB), Galveston. The institutional review board (IRB 18-0073) at UTMB approved the study and waived the need for consent. **Inclusion and Exclusion Criteria:** The electronic medical record

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for all infants born at our center between 1st January 2017 and 30th July 2018 was reviewed (n=221). Infants with birth weight ≤1500 g and ≤30 weeks gestational age who were admitted to the neonatal intensive care unit were included in the study (n=201).Infants with known lethal chromosomal or congenital abnormalities, necrotizing enter colitis, or spontaneous intestinal perforation were excluded from the study.

Study groups: The study population was divided into the diuretic group (infants who received hydrochlorothiazide and spironolactone for BPD for ≥7 days), and the control group (infants who did not receive diuretics). Their hospital course was reviewed for the development of MBD before, during, and after the start of diuretics.

Definition of BPD: BPD was defined as infants requiring respiratory support at 36 weeks postmenstrual age [13].

Definition of MBD: Parathyroid hormone (PTH) levels > 100 IU/L and X-ray evidence of fraying and irregular femoral metaphysic.

Screening of MBD: In our center, routine screening for MBD is done at 4 weeks postmenstrual age for infants born at ≤34 weeks of gestation. These neonates undergo screening for MBD which includes serum calcium, phosphorus, alkaline phosphatase (ALP), PTH, Vitamin A levels and X-Rays of bilateral knees. PTH >100 IU/Lis considered significant for MBD and knee X-rays, 25-hydroxy Vitamin D levels are obtained, and calcium bicarbonate supplementation is started. The PTH level is then obtained every 2 weeks until 2 consecutive PTH values are <100 IU/L. Evidence of femur demineralization and irregular metaphyseal edges are considered positive for MBD on radiographic imaging.

Data collection

Chart review was performed, and clinical data included gestational age, birth weight, gender, diagnosis of BPD, duration of parenteral nutrition, IUGR, comorbidities, history of metabolic bone disease, diuretic use, mean days on various respiratory support, X-ray findings and sodium supplementation were noted. Maternal characteristics such as history of infection, chorioamnionitis, premature prolonged rupture of membranes, chronic hypertension or pregnancy-induced hypertension, use of antenatal steroids were also collected.

Statistical analysis: Statistical analyses were carried out using SPSS. Procedures used included Chi-Square test and t-test. Multivariate analysis was done using likelihood ratio forward stepwise method. The level of statistical significance was set at $p < 0.05$.

Results

During the study period from January 2017 to August 2018, 201 neonates ≤ 30 weeks of gestation at the time of birth, and with birth weight ≤1500 grams were included in the study. Of these, 68 neonates received diuretics for BPD for ≥ 7 days, and 133 neonates did not (control group) (Figure 1). The mean gestational age of the infants in the diuretic group was 26.31 weeks ± 1.7 days vs. 28.21 weeks ± 2.8 days in the control group. The maternal demographics for the two groups are summarized in (Table 1). A significant number of PI in the diuretic group had maternal history of prenatal steroid administration (60.2% vs. 39.8% respectively). The infants in the diuretic group were significantly younger (26.31 weeks ± 1.7 days vs. 28.21 weeks ± 2.8 days in the control group) and smaller (857 ± 240 grams vs 1045 ± 311 grams in the control group and had a significantly higher incidence of comorbidities such as BPD, MBD, intraventricular hemorrhage and patent ductus arteriosus (Table 2). Multivariate logistical regression analysis was done for the significant variables from the univariate analysis which showed that use of diuretics for BPD, extremely low birth weight (<1000 grams), BPD and chorioamnionitis were independently associated with the risk of MBD between the two groups (Table 3).

Our study showed that a significant number of neonates developed MBD after starting diuretics (41% vs. 33%, p=0.017) (Table 4).The

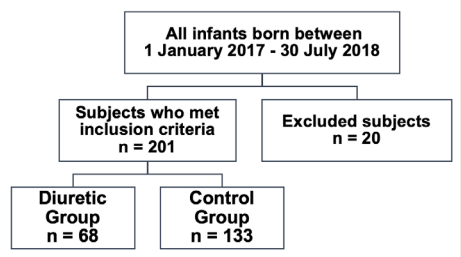

Figure 1: Study population assessed for development of MBD.

Table 1: Maternal characteristics

n (%)	Diuretic Group (n=68)	Control Group (n=133)
Prenatal Care	62 (92.5)	123 (92.6)
Prenatal Steroid	41 (60.2) *	52 (39.8)
Antenatal Antibiotics	12 (17.9)	40 (30.3)
Antenatal Magnesium	24 (35.3)	44 (33.3)
PPROM	24 (35.8)	27 (20.5)
ROM > 18 hours	19 (27.7)	27 (20.5)
PIH/HTN/chronic HTN	28 (41.8)	63 (47.9)
Chorioamnionitis	60 (8.8)	10 (7.4)
Substance Abuse	12 (18.2)	30 (22.7)
HIV positive	0	2 (1.7)

PPROM: Prolonged premature rupture of membranes, ROM: rupture of membranes, PIH: pregnancy induced hypertension, HTN: hypertension; * p<0.005

Table 2: Neonatal characteristics

Mean ± SD (%) or n (%)	Diuretic Group (68)	Control Group (133)
Mean gestational age (weeks)	26.31 ± 1.73*	28.21 ± 2.75
Mean Birth weight (grams)	857 ± 240*	1045 ± 311
Males	46 (67.6)	67 (50.8)
BPD	60 (88.2) *	16 (12.2)
Parenteral nutrition > 4 weeks	32 (47.1) *	22 (16.4)
IUGR	17 (25.0)	32 (24.4)
Postnatal steroids > 1 week	26 (38.2) *	9 (6.5)
ROP	64 (94.1) *	49 (36.6)
IVH	16 (23.5) *	11 (8.1)
PDA	26 (38.2) *	27 (20.3)
Mean days on respiratory support	13.13 ± 15.43*	8.63 ± 8.41
Mean days on CMV	20.53 ± 31.70*	5.04 ± 10.80
Positive knee X-ray	33 (48.4) *	31 (23.3)
Sodium supplementation	30 (44.8) *	16 (11.9)

BPD: bronchopulmonary dysplasia, IUGR: intrauterine gestational restriction, ROP: retinopathy of prematurity, IVH: intraventricular hemorrhage, PDA: patent ductus arteriosus, CMV: conventional mechanical ventilation; * p< 0.05

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Table 3: Multivariate analysis of demographics

Variable	95% CI of OR	Odds ratio (OR)	P value
Diuretics for BPD	1.14 – 3.95	2.121	< 0.05
ELBW infants (<1000 grams)	2.83 – 11.49	5.706	< 0.001
BPD	1.78 – 6.33	3.36	<0.001
Chorioamnionitis	1.62 – 15.36	5	< 0.005
BPD: bronchopulmonary dysplasia, ELBW: extremely low birth weight babies			

Table 4: Association of diuretic use with development of MBD

n (%) p-value	Diuretic Group (68)	Control Group (133)	p-value
MBD	28 (41.2) *	33 (24.8)	0.017
MBD after diuretic use	16 (23.5)*	1 (0.8)	<0.001
MBD: metabolic bone disease; Pearson $\chi^2 = 5.70$			

Table 5: Respiratory outcomes of neonates

Mean ± SD	Diuretic Group (68)	Control Group (133)	P value
Duration of initial ventilation (days)	13.1 ± 15.4*	8.6 ± 8.4	0.010
Duration of MV (days)	20.5 ± 31.7n *	5.0 ± 10.8	< .001
Duration on CPAP/ SiPAP (days)	37.7 ± 18.7*	18.9 ± 13.8	< .001

duration of initial days of mechanical ventilation (13.1 ± 15.4 days vs. 8.63 ± 8.41 days in the control group, p=0.010) as well as total days of mechanical ventilation (20.5 ± 31.7 vs.5.0 ± 10.8 days, p<0.001) were significantly higher in the diuretic group compares to the control group (Table 5). Similarly, the number of days of positive-pressure ventilation i.e. continuous positive-pressure ventilation or biphasic positive-pressure ventilation were also higher in the diuretic group. We attempted to measure improvement in FiO2 requirement in these neonates, which was limited by changes in modes of ventilation and not amenable to statistical analysis.

Discussion

Our study showed that PI who receive diureticsfor BPD have significantly higher rates of MBD(23% vs 0.8% p<0.001). This could be confounded by the likelihood that such neonates are comparatively more premature, have lower birth weight and worse respiratory disease, but multivariate analysis confirmed that the high rate of MBD in the diuretic group was independent of gestational age. The study by Orth et al suggested that the timing of starting diuretics did not affect the onset of MBD, and the total cumulative dose of furosemide may be associated with a higher incidence of MBD [11]. We studied the onset of MBD in PI after diuretic use for ≥7 days and did find higher rates of MBD in these infants after diuretic use compared to the control groups.

Despite advances in parenteral and enteral nutrition modalities for premature neonates, MBD continues to be a significant co-morbidity of prematurity. MBD is defined as decreased bone mineralization, and its biochemical and diagnostic criteria varies from center to center. Our center uses PTH as the biomarker for MBD screening, and it has been shown to be more sensitive than ALP in a previous study at our institute [14].

Premature infants lose the potential accretion of approximately 2.3-2.98 mmol/day of calcium and 1.9-2.98 mmol/day of phosphorus due to their preterm birth [17,15] This lack of accretion makes them more vulnerable to developing MBD than term infants. In addition, pathophysiology of MBD in premature infants is multifactorial [8,15]. Immature digestive system, use of total parenteral nutrition, use of diuretics for fluid retention, congestive heart failure, mineralocorticoid use for adrenal insufficiency, lack of mobility and hormone imbalance also contribute to MBD [16] .Conditions affecting placental transport of nutrients such as chorioamnionitis and IUGR are also associated with high risk of MBD due decreased in utero phosphate transport (16,17). In our study, the presence of chorioamnionitis increased the odds of MBD by five times (CI 1.65-15.36, p <0.005). A higher incidence of postnatal MBD has been noted in infants with IUGR in the study by Montaner Ramón et al [17], however due to a smaller sample size we did not find this association.

A study of 835 infants from the prematurity and respiratory outcomes program (PROP) did not show any improvement in long term respiratory outcomes of infants when diuretics were used for BPD [18]. Furosemide was the diuretic used in majority of these patients whereas we studied hydrochlorothiazide and spironolactone use, which are widely used for chronic management due to their comparatively safer adverse effect profile.

Interestingly, the PROP study noted an increase in the need for respiratory support in patients 1-7 days after receiving diuretics. Our study supported these findings, as the mean duration of mechanical ventilation as well as positive pressure ventilation was higher in the diuretic group than the control group.

Across the US, 1/3rd premature infants <1500 grams birth weight receive diuretics for BPD with a wide variation across the neonatal centers [5]. This wide variation is because of potential adverse effects of diuretics along with a lack of medical evidence of the timing, appropriate dose, correct indication, and most importantly, level of efficacy for the prevention of BPD. No randomized controlled trials of diuretics use to prevent BPD have been done.

The results of our study are limited by its small sample size. Though this is the first study to establish an increased risk of MBD in PI after treatment with diuretics, these results need to be validated by larger multicenter studies. Secondly, there is no standard definition of MBD across centers, and different biomarkers are used in PI to diagnose MBD. Our study used PTH to define presence of MBD, which may not be a standard practice in other centers. Finally, our study did not record the effect of diuretic use on MBD over long-term follow-up. Longitudinal studies will help to establish the clinical implications of MBD associated with diuretic use in PI.

Conclusion

Preterm infants treated with hydrochlorothiazide and spironolactone for BPD are more likely to develop MBD after diuretic use without any significant improvement in respiratory status. Diuretic use in premature infants did not decrease the mean duration of mechanical ventilation and positive pressure ventilation compared to the control group. Diuretics should be used with caution and monitored closely for MBD.

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Ethics Approval

The study was approved by the Institutional Review Board at the University of Texas Medical Branch, Galveston, TX. Need for consent was waived. The study was performed in accordance with the Declaration of Helsinki.

Contributor's Statement

Drs. Snigdha Bhatia and Sunil K Jain conceptualized and designed the study, coordinated and supervised data collection, and critically reviewed the manuscript for important intellectual content.

Drs. Snigdha Bhatia, and Maria J Abraham collected the data and reviewed and revised the manuscript.

Drs. Mohammad Q Mehdi and Bruce Niebuhr carried out the statistical analysis.

All authors approved the final manuscript as submitted and agree to be accountable for all aspects of the work.

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