Impact of Early Versus Late Diuretic Exposure on Metabolic Bone Disease and Growth in Premature Neonates

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OBJECTIVES This study aimed to determine whether there are differences in the incidence of metabolic bone disease (MBD) between preterm neonates first exposed to diuretics prior to 2 weeks of life versus those exposed after 2 weeks.

METHODS This study was a retrospective analysis of premature neonates born at a tertiary care center between 2011 and 2015 who received either furosemide or chlorothiazide. The primary outcome was incidence of MBD. Secondary outcomes included growth, electrolyte disturbances, oxygen requirement, and length of stay.

RESULTS A total of 147 patients were included. Early initiation (n = 90) and late initiation (n = 57) arms were balanced with respect to birth weight and gestational age. There was no difference in incidence of MBD in the early group (76%) versus the late group (65%; p = 0.164). Stratification by cumulative dose showed incidence of 85% in patients receiving ≥ 8 mg/kg of furosemide, compared with 68% and 64% of those in the <4 mg/kg and 4 to 7.9 mg/kg strata, respectively (p = 0.06). The early group experienced greater reductions in length-for-age growth during diuretic therapy (−70% versus −40%; p = 0.009). Electrolyte abnormalities were more prevalent in the early group. Although there was no difference in duration of mechanical ventilation, duration of supplemental oxygen requirement was reduced in the late group (75 versus 89 days; p = 0.003).

CONCLUSIONS Timing of diuretic initiation did not affect incidence of MBD. Increased cumulative furosemide exposure may be associated with higher incidence. Patients first exposed to diuretics within 2 weeks of life are at higher risk for electrolyte abnormalities and reduced growth velocity.

ABBREVIATIONS ALP, alkaline phosphatase; DOL, day of life; MBD, metabolic bone disease; MV, mechanical ventilation; NICU, neonatal intensive care unit; PNA, postnatal age; VLBW, very low birth weight

KEYWORDS chlorothiazide; diuretics; furosemide; metabolic bone disease; neonates; premature

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Introduction

Metabolic bone disease (MBD) of prematurity is a complex and multifactorial condition characterized by a reduction in organic protein matrix or bone mineral content, with or without rachitic changes.^{1,2} The disease occurs in up to 23% of newborns weighing less than 1500 g at birth and 55% of those born at a birth weight of less than 1000 g.¹ Likewise, gestational age is inversely proportional to the risk of the disease.^{1,3} Modifiable risk factors shown to contribute to the development of MBD include inadequate nutrient intake (most notably calcium, phosphorus, and vitamin D), prolonged duration of parenteral nutrition, immobilization, and exposure to medications such as diuretics and steroids.^{3,4} Additionally, because approximately 80% of bone mineralization occurs during the third trimester of pregnancy, preterm infants are at increased risk for osteopenia even when

supplemented with phosphorus and calcium.^{5,6}

In the neonatal population with respiratory disease, diuretics are used frequently within the first month of life. Rationale for their use in this population is derived from observations that increased fluid collection in alveolar and interstitial lung spaces results in impaired gas exchange.⁷ Although single doses of furosemide (Lasix, Sanofi-Aventis US, Bridgewater, NJ) and chlorothiazide (Sodium Diuril, Akorn, Lake Forest, IL) have been linked to short-term increases in pulmonary compliance, data supporting improved outcomes beyond 24 hours following administration are not found in the literature. No randomized controlled trial has demonstrated improvement in mortality, duration of oxygen supplementation or mechanical ventilation, length of stay, or incidence of subsequent chronic lung disease resulting from the use of these agents.^{8,9}

In addition to a lack of data supporting their use in

respiratory disease, early or ongoing use of diuretics is associated with many potentially significant adverse effects, including nephrocalcinosis, bone demineralization, and electrolyte abnormalities.⁸ By stimulating urinary excretion of sodium and water, diuretics may markedly reduce renal reabsorption of divalent cations, due to reliance on the active transport of sodium and chloride. As a result of this reduced reabsorption, thiazide diuretics have been shown to contribute to osteomalacia through hypophosphatemia via increased renal clearance of inorganic phosphate. Prolonged use of loop diuretics causes hypocalcemia, resulting in elevation of circulating parathyroid hormone and accelerated bone remodeling.^{1,10,11}

Presently, there are no studies that directly examine the relationship between diuretics and MBD as a primary objective. Results from several studies have, however, exhibited associations between diuretic exposure and varying degrees of bone disease. In 2014, a large retrospective analysis of the clinical characteristics of extremely low birth weight (birth weight ≤ 1000 g) infants with MBD found that average duration of furosemide therapy was increased 86% in those patients with MBD compared with a control group without the disease.² Two additional retrospective reviews from 2012 and 1988 noted diuretic use for a duration longer than 2 weeks was present in 42% of preterm infants with rib fractures and 75% of those with spontaneous fractures, respectively.^{5,12} A retrospective study in 2012 reviewed premature neonates with posterior rib fractures and found that 89% of patients developing these fractures were previously treated with multiple doses of diuretics.⁶ Most recently, in 2016, Jensen and colleagues³ retrospectively reviewed preterm infants with severe bronchopulmonary dysplasia to determine that both exposure to furosemide and duration of furosemide therapy were associated with greater risk for severe MBD.

Due to known osteopenic effects of diuretics and the previously described delayed bone mineralization that occurs during normal neonatal development, the aim of this study was to evaluate the effect of the timing of diuretic initiation on the incidence of metabolic bone disease in very low birth weight (VLBW; birth weight ≤ 1500 g) infants. Because fetal nephrogenesis continues to occur until approximately 36 weeks gestational age, we hypothesized that earlier exposure to renally excreted diuretics previously shown to contribute to the development of MBD in neonates may increase risk for the disease.⁷

Materials and Methods

Study Design. A single-center retrospective chart review was conducted to evaluate the effects and outcomes of exposure to consecutive doses of diuretics within the first month of life. All patients admitted to the institution's neonatal intensive care unit (NICU)

between July 1, 2011, and July 31, 2015, who received a dose of diuretics at dosing weight <1500 g were screened for inclusion. This study window corresponds with the first use of fully electronic medical record software at this institution. Patients born at less than 32 weeks gestational age, with birth weight less than 1501 g, and who were treated with 2 or more doses of furosemide or chlorothiazide within the first 28 days of life were eligible for inclusion in the study. Criteria for exclusion included major congenital anomaly, and death or transfer from the NICU prior to 8 weeks of life. Patients were divided into "early initiation" or "late initiation" cohorts according to day of life when second diuretic dose was administered, with inclusion of day 14 in the early initiation arm. This study was approved by the hospital's Institutional Review Board, and informed consent was not required.

End points. The primary objective was to determine whether incidence of MBD varied between VLBW infants with early exposure to diuretics compared with those exposed after 2 weeks of life. The primary outcome of MBD was defined by a single serum alkaline phosphatase (ALP) level greater than 500 IU/L, clinical diagnosis of osteopenia or rickets, or radiologic evidence of fracture as determined by the institution's radiologists. Incidence of the primary outcome was assessed from diuretic initiation through first hospital discharge or mortality. Additional analysis was conducted to evaluate for potential associations between incidence of MBD and cumulative weight-based diuretic doses as described *a priori*. Weight-based dose calculations used patients' weight at the time of prescribing. Patients were stratified by furosemide dosage into the following groups based on cumulative intravenous dose received: <3.9 mg/kg, 4 to 7.9 mg/kg, and ≥ 8 mg/kg. For patients receiving enteral furosemide doses at any time, a 2:1 ratio was used to convert from enteral to intravenous dose. For chlorothiazide, patients were stratified into dosing groups of <150 mg/kg or ≥ 150 mg/kg. All chlorothiazide doses assessed during the study window were administered via enteral route. Secondary outcomes assessed include growth velocity, electrolyte disturbances, duration of oxygen and ventilation requirements, and length of stay. Growth velocity was defined by change in age-based population percentiles for weight, length, and head circumference using Fenton growth charts for preterm infants. Standard practice at this institution is for height, weight, and head circumference to be recorded in the electronic medical record at least weekly for all patients admitted to the NICU. Growth percentiles were assessed at diuretic initiation and discontinuation; the relative percent difference between these 2 values was reported as growth velocity. Likewise, relative percent differences in serum electrolyte levels were evaluated from diuretic initiation to discontinuation. Duration of oxygen supplementation and mechanical ventilation were measured from the

Figure. Patient enrollment and disposition.

DOL, day of life

time of first diuretic use to the discontinuation of each respective respiratory therapy or hospital discharge.

Statistical Analysis. Patient demographics were evaluated using descriptive statistics. Statistical analysis was performed for all categorical data outcomes using χ^2 or Fisher exact testing, and continuous variables were analyzed using paired or 2-sided *t*-tests as appropriate. Descriptive statistics were reported as mean $\pm$ SD if normally distributed, or median with IQR if non-normally distributed. Statistical analysis was performed using JMP Pro software (SAS Institute Inc, Cary, NC). Significance was defined as $p \leq 0.05$ throughout the study.

Results

A total of 294 patients receiving diuretics during the study window were screened for inclusion in the trial. A total of 147 patients were deemed eligible for analysis following application of enrollment criteria, as outlined in the Figure. Of these 147 patients, 90 received consecutive doses of furosemide or chlorothiazide up to and including postnatal age (PNA) 14 days, whereas the remaining 57 did not receive consecutive doses of diuretics until the PNA of 15 to 28 days. Early and late initiation arms were well balanced with regard to birth weight, gestational age, 5-minute Apgar scores, antenatal corticosteroid exposure, and age-based growth percentiles for both weight and length (Table 1). The early initiation group contained a higher propor-

tion of males than the late group (63% versus 44%; $p = 0.021$). Mean PNA at diuretic initiation of patients in the early initiation arm was 9.7 days, whereas mean PNA at diuretic initiation in the late arm was 20.3 days. Only 1 patient did not require oxygen supplementation at the time of diuretic initiation. Mechanical ventilation, however, was used more frequently at diuretic initiation in the early group (91%) than in the late (68%; $p < 0.001$).

There was no significant difference between incidence of MBD between patients in the early group (75.6%) versus those in the late (64.9%; $p = 0.164$). One or more serum ALP levels ≥ 500 IU/L most frequently contributed to the diagnosis of MBD in both arms (86%). A total of 49% of all patients developed evidence of osteopenia, rickets, or fracture on imaging, and roughly 21% of all patients met both components of criteria for diagnosis.

All but 1 patient included in the study received 2 or more doses of furosemide during the first 28 days of life. A total of 29 patients received consecutive doses of both furosemide and chlorothiazide during that time, whereas the remaining 1 patient received chlorothiazide alone. Stratification of primary outcome results by drug(s) received revealed no difference between early and late group MBD incidence in patients receiving furosemide alone or furosemide with chlorothiazide (Table 2). Additional stratification of MBD incidence by cumulative milligram per kilogram diuretic dose received showed increased incidence in those patients

Table 1. Patient Demographics

	Early Initiation (n = 90)	Late Initiation (n = 57)	p value
Birth weight, g*	787 ± 198	775 ± 210	0.49
Gestational age, wk*	26.1 ± 2.1	26.1 ± 1.7	0.65
Male sex, n (%)	57 (63)	25 (44)	0.021
Apgar score at 5 min†	6 (4–7)	6 (4–8)	0.65
Maternal antenatal corticosteroid use, n (%)	58 (64)	39 (68)	0.62
PNA at diuretic initiation, days*	9.7 ± 2.9	20.3 ± 3.8	—
Weight-for-age at diuretic initiation, percentile†	27.4 (16–54)	23.6 (13–45)	0.43
Length-for-age at diuretic initiation, percentile†	32.6 (14–59)	32.6 (7–57)	0.56
MV at diuretic initiation, n (%)	82 (91)	38 (68)	<0.001
Supplemental oxygen at diuretic initiation, n (%)	89 (99)	57 (100)	0.42

MV, mechanical ventilation; PNA, postnatal age

* Mean ± SD.

† Median (IQR).

receiving ≥ 8 mg/kg of furosemide (85%) compared with those in the < 4 mg/kg (68%) and 4 to 7.9 mg/kg strata (64%; $p = 0.06$), but this increased rate was not statistically significant. There was no difference in incidence of MBD between patients receiving cumulative chlorothiazide dose < 150 mg/kg versus those receiving ≥ 150 mg/kg (79% versus 73%; $p = 0.7$).

Patients in the early group experienced a larger relative growth reduction than the late group with regard to length-for-age percentiles during the course of diuretic therapy (median, -70.2% and -39.9% ; $p = 0.009$), but weight-for-age changes were similar between groups (-38.7% versus -23.7% ; $p = 0.17$). Median observed decrease in serum electrolyte levels from baseline was greater in the early initiation group with regard to sodium (-5.9%) and calcium (-8.3%) than in the late group (-3.7% and -6.5% , respectively; $p = 0.001$), with similar rates of enteral supplementation for correction required between the 2 arms (32% versus 30%; $p = 0.76$; Table 3). Although there was no difference in duration of mechanical ventilation ($p = 0.089$), duration of supplemental oxygen requirement was reduced in the late group compared with the early group (74.6 days versus 89.4 days; $p = 0.003$). Duration of diuretic therapy was longer in the early group (17.5 days) compared with the late group (11 days; $p < 0.001$). There was no difference in length of stay between the 2 groups ($p = 0.622$).

Discussion

Although overall survival of VLBW infants has improved substantially during the past 2 to 3 decades in congruence with advances in neonatal care, it is estimated that 63% of infants born at a gestational age of 28 weeks or less still experience significant morbidities prior to discharge from the hospital.¹³ Although published studies related to MBD are limited,

it has previously been reported that the disease occurs in up to 23% and 55% of VLBW and extremely low birth weight infants, respectively.¹ The incidence of MBD in patients receiving prolonged diuretic therapy has not previously been described in the literature. The overall frequency of MBD in our study of VLBW infants exposed to multiple doses of furosemide or chlorothiazide was 71.4%. This increased incidence supports the secondary findings of several previous studies suggesting that the use of diuretics does contribute to development of MBD in neonates.^{2,3,5,6,12} Our study is the first to further evaluate whether the timing of diuretic initiation impacts MBD incidence or contributes to impaired growth within this population.

The baseline characteristics of our patient population were similar to those reported in the literature.^{2,3,5,6,12} The early and late initiation groups were well balanced in most regards (Table 1). It is not likely that the increased percentage of males in the early initiation arm contributed in any way to patient outcomes. Although the early initiation cohort's increased rate of mechanical ventilation at diuretic initiation was statistically significant, we suspect this was likely the result of inherent pulmonary immaturity related to PNA at the time of diuretic initiation. In the later initiation group, the patients were older (20.3 versus 9.7 days), allowing them additional time to reach developmental appropriateness and readiness for extubation. Extubation criteria at our institution are based on achievement of sustained weaning to minimal ventilator settings and provider discretion. Once it is deemed that a patient's clinical status is optimal for successfully maintained extubation, mechanical ventilation may be discontinued. We believe the late initiation group likely would have displayed a similar rate of mechanical ventilation if observed 10 days prior, primarily because of the decreased mechanical and

Table 2. Primary Outcome

	Early Initiation (n = 90)	Late Initiation (n = 57)	p value
MBD, n (%)	68 (76)	37 (65)	0.16
Component of MBD diagnosis met, n (%)			
Serum ALP $\geq$ 500 IU/L	62 (69)	34 (60)	0.25
Diagnosis via imaging	26 (29)	15 (26)	0.74
Both components met	21 (23)	10 (18)	0.40
MBD stratified by drug received, n (%)			
Furosemide alone (n = 117)	53 (73)	29 (66)	0.44
Chlorothiazide alone (n = 1)	—	1 (100)	—
Both (n = 29)	15 (88)	7 (58)	0.09
MBD stratified by cumulative dose received, n (%)			
Furosemide, <4 mg/kg (n = 47)	32 (68)		
Furosemide, 4–7.9 mg/kg (n = 58)	37 (64)		0.06
Furosemide, ≥ 8 mg/kg (n = 41)	35 (85)		
Chlorothiazide, <150 mg/kg (n = 19)	15 (79)		
Chlorothiazide, ≥ 150 mg/kg (n = 11)	8 (73)		0.70

ALP, alkaline phosphatase; MBD, metabolic bone disease

tensile strength of pulmonary tissue and musculature resulting from age-related immaturity.

Although bone disease is well recognized as a common complication of preterm birth within the neonatal population, universally recognized criteria for the diagnosis of MBD have not been established in the medical community to date.⁴ Screening for MBD has been historically controversial, because clinical examination is generally only capable of detecting advanced disease, whereas a single reliable biochemical diagnostic technique has been difficult to ascertain. Previous studies have identified serum ALP as potentially the most useful metabolic marker for MBD, and in a large study of 336 preterm infants, Figueras-Aloy and colleagues¹⁴ found that serum ALP >500 IU/L corresponded best with reduced bone mineral density for diagnosis of the disease. Although bone-specific ALP is the dominant ALP isoform present in childhood, additional isoenzymes of ALP exist and contribute to total ALP as measured in the serum. Thus, measurement of total ALP inherently fails to differentiate between bone and hepatic sources and may present challenges for its use as a surrogate marker.^{15,16} The lack of unanimous criteria for diagnosis may somewhat limit the generalizability of our findings, but we feel the criteria used in our study are appropriate based on the current state of the literature. Unfortunately, these criteria do rely on additional radiologic subjectivity, for which we were unable to identify or control.

Because of the late completion of nephrogenesis, which is not concluded until approximately the 36th week of gestation in the human fetus, we hypothesized

that earlier exposure to renally excreted medications known to contribute to the development of MBD in neonates may increase risk for the disease.⁷ In this study, findings showed the incidence of MBD was not statistically higher in patients receiving diuretics within the first 2 weeks of life versus those with later initial exposure. In a review of the literature, numerous previous studies have determined that larger cumulative doses of both furosemide and thiazides are a risk factor for the development of nephrocalcinosis within the neonatal population.^{17–19} Because of these findings, we were also interested in the relationship between cumulative diuretic doses and MBD. When stratified by cumulative weight-based dose received, patients receiving less than 150 mg/kg chlorothiazide showed no difference in incidence versus those receiving large doses. Among patients receiving furosemide, however, we found a trend toward increased MBD incidence in those patients receiving cumulative doses of ≥ 8 mg/kg (85%), versus those receiving <4 mg/kg or 4 to 7.9 mg/kg (68% and 64%, respectively). This variance between furosemide dosage stratifications was not statistically significant, but it raises questions about differences that may be observed in a larger sample size. Although dosage stratification intent for both chlorothiazide and furosemide was described *a priori*, the dosing strata used were selected arbitrarily and without direct scientific guidance. Based on these findings, however, and with the understanding that nephrogenesis is incomplete in preterm neonates, we feel it is reasonable to suggest limiting neonatal furosemide exposure to the lowest cumulative doses necessary during the

Table 3. Secondary Outcomes

	Early Initiation (n = 90)	Late Initiation (n = 57)	p value
Growth velocity			
Weight-for-age, % reduction*	38.7 (8.2–61.1)	23.7 (0–54.3)	0.17
Length-for-age, % reduction*	70.2 (42.5–88.7)	39.9 (16.1–68)	0.009
Serum electrolyte changes			
Na ⁺ change from baseline, %*	–5.9 (–10.3 to –3.2)	–3.7 (–7.8 to –0.7)	0.001
K ⁺ change from baseline, %*	–10.1 (–24.8 to 0)	–11.9 (–26 to 2.4)	0.18
Ca ²⁺ change from baseline, %*	–8.3 (–17.5 to –2.9)	–6.5 (–11.1 to 0)	0.001
PO ₄ ^{3–} change from baseline, %*	–16.2 (–30.4 to 0)	–18.2 (–38 to 5.3)	0.11
Enteral supplementation required, n (%)	29 (32)	17 (30)	0.76
O ₂ requirements			
Duration of MV, days*	28 (18–40)	24 (10–35)	0.089
Duration of O ₂ supplementation, days*	88 (66–112)	67 (44–92)	0.003
Duration of diuretic therapy, days*	17.5 (13–21)	11 (6–15)	<0.001
Length of stay, days†	111 ± 34	109 ± 36.4	0.62

Ca²⁺, calcium; K⁺, potassium; MV, mechanical ventilation; Na⁺, sodium; O₂, oxygen; PO₄^{3–}, phosphate

* Median (IQR).

† Mean ± SD.

first month of life.

Although the primary outcome of MBD was not observed more frequently in the early initiation group, those patients receiving diuretics within the first 2 weeks of life experienced several other undesired effects in our study. Patients in the early group experienced greater relative losses of serum sodium and calcium, an effect that has been reported previously in the literature in the VLBW population.²⁰ Only 1 patient in the present study received chlorothiazide without furosemide. Characteristically, renal calcium excretion is expected to decrease with chlorothiazide use because of the drug's mechanism. When used in combination with furosemide, however, Campfield and colleagues²⁰ reported that the addition of a thiazide diuretic failed to counteract furosemide's calciuric effect, and speculated that the calciuric influence of sodium received by many preterm infants would overwhelm the thiazide's calcium-sparing mechanism. We are unable to meaningfully assess the possibility that chlorothiazide alone would result in a lesser magnitude of electrolyte losses than those observed in this study, but this should be considered for future analysis. Additionally, this study was not able to control for enteral or parenteral supplementation of electrolytes in the analysis of MBD incidence, but our institution does use a standardized method for supplementation that should have limited nutritional deviations between the 2 treatment cohorts. Other confounding variables, including nutritional content of breast milk with or without fortification, may have influenced the outcomes observed.

In addition to electrolyte abnormalities, the early

initiation group experienced a greater reduction in growth velocity with respect to length compared with those in the late initiation arm. The availability of recorded length and weight measurements during the course of each patient's hospitalization allowed for assessment of growth trends during this period. By plotting these measurements on the revised Fenton growth charts for preterm infants, we were able to calculate deviations from expected growth velocity using changes in age-based growth percentile from the time of diuretic initiation to diuretic discontinuation or hospital discharge. Previous studies have revealed a variety of potential causes for reduced intrauterine growth and later development rate, such as repeated antenatal corticosteroid treatments, maternal smoking status, maternal parity, and gestational diabetes or hypertensive status.^{21,22} Incidence of treatment with antenatal corticosteroids was similar between the early and late initiation cohorts in this study (Table 1). However, data related to frequency and timing of antenatal corticosteroid administration were not collected. These variables, as well as those related to the additional maternal information mentioned above, may have played a role in the growth findings of this study. Although both early and late initiation arms experienced trends toward reduced growth velocity for both height and weight, the early initiation arm showed a larger mean reduction from expected length than its late initiation counterpart. When viewed with other findings of this study, it may be proposed that such observations as increased electrolyte losses may contribute to reduced bone development with respect to length. This study

is the first to analyze such growth-related outcomes as they relate to diuretic use. It is important to note, however, that other drug classes, including steroids and methylxanthines, may also impair calcium regulation, thus reducing bone mineralization.^{1,3} Data related to concurrent administration of these medications were not assessed in this study, but additional studies assessing similar growth-related outcomes in neonates receiving extended therapy with these agents may be beneficial.

Although the timing of the initiation of diuretics was not shown to significantly alter the incidence of our primary outcome, we did find that the duration of diuretic therapy was 59% longer for patients in the early initiation cohort (Table 3). As mentioned previously, the findings of several studies in the literature have associated duration of diuretic therapy with an increased risk for varying degrees of bone disease.^{2,3,5,12} In light of these findings, it is important to note that the differences in electrolyte and growth-related outcomes detected between our study cohorts may also be driven by the observed difference in duration of therapy, rather than the timing of diuretic initiation. This would furthermore support the hypothesis that cumulative diuretic doses may contribute to increased MBD risk. The study conducted by Jensen and colleagues³ additionally identified corticosteroid duration as a risk factor for severe MBD, but was unable to assess the risk associated with increasing cumulative doses of furosemide or steroids. We believe that additional trials assessing such outcomes could yield clinically meaningful results.

One final secondary outcome of interest to our group was that of the pulmonary benefit of diuretic use in our population. As discussed previously, no evidence of improvement in duration of oxygen supplementation or mechanical ventilation has previously been demonstrated in the literature.^{8,9} In spite of this, a 2011 survey of 400 neonatologists conducted by Hagadorn and colleagues⁸ found that respondents opted for diuretic therapy in more than 30% of theoretical clinical scenarios involving VLBW infants with respiratory disease. These respondents cited expectations for improvement in long-term pulmonary mechanics and decreased ventilation days as benefits of diuretic therapy. In our study, we observed no difference in duration of mechanical ventilation or length of stay between the 2 treatment arms. Duration of supplemental oxygen requirement, however, was decreased by 21 days in those patients first receiving diuretic therapy after the first 2 weeks of life. Although this does not suggest that delaying diuretic use causes clear pulmonary benefit in patients with respiratory disease, it does provide evidence that any theoretical respiratory benefit of diuretic use is not lost by delaying therapy. We believe this to be an important finding when considering the use of these agents in the early days of life.

Our study does have several limitations with respect

to design and statistical interpretation that should be considered. This is a retrospective single-center analysis, and as such may be susceptible to selection or misclassification bias. Because of its retrospective nature, it is disposed to confounding for which we were unable to control, including difficult-to-measure nutritional variations, varying degrees of baseline lung dysfunction, subjectivity associated with the radiologic aspect of our primary outcome, and exposure to alternate agents, such as steroids, which have previously been shown to contribute to outcomes included in our study. There is currently no universally accepted definition for MBD, and the use of ALP as a surrogate marker for bone disease also presents several challenges. Additionally, the study does not assess other interventions that may influence ALP production or excretion, and it cannot be ascertained whether elevations in total serum ALP were affected by the presence of hepatic dysfunction, impaired nutritional status, or endocrinologic disorders that were not evaluated in our study. Next, arbitrary selection of the doses used for cumulative diuretic stratification, although specified *a priori*, did represent a design flaw. Finally, although our results do suggest differences between early and late initiation cohorts with respect to growth velocity and electrolyte abnormalities, these associations have not been adjusted for multiple comparisons and may lack true statistical significance.

Conclusion

This study identified no statistically significant differences between the incidence of MBD in patients receiving consecutive diuretic doses during the first 2 weeks of life versus those initiated on diuretics after 2 weeks of life. Results did indicate, however, that early initiation may increase the magnitude of electrolyte abnormalities in premature neonates and may reduce growth velocity with respect to length. Late initiation does not appear to cause any loss of the theoretical pulmonary benefits of diuretic therapy in patients with respiratory disease. These findings should be taken into consideration when determining the necessity of diuretic therapy in VLBW infants within the first month of life. A larger, prospective, randomized trial is warranted to validate these results and to aid in determining their impact on clinical practice.

ARTICLE INFORMATION

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