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Variables Which Impact Fluid and Electrolyte Management in The Neonatal Intensive Care Unit and Associations with Neonatal Outcomes

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Abstract

Objective: Managing fluids in extremely premature infants is challenging due to the delicate balance required between nutrition, organ perfusion, and avoiding fluid overload. This study aims to evaluate how early fluid management strategies affect morbidity and mortality outcomes in these neonates.

Study Design: This retrospective observational study focused on infants born at ≤28 weeks gestation at a level 3 neonatal intensive care unit (NICU). We analyzed demographic, clinical, and laboratory data from the first two weeks of life to assess current fluid management practices. The study examined correlations between total daily fluid intake and morbidities such as bronchopulmonary dysplasia (BPD), hemodynamically significant patent ductus arteriosus (PDA), necrotizing enterocolitis (NEC), intraventricular hemorrhage (IVH), and mortality. Additionally, we explored the impact of early postnatal weight loss on these outcomes.

Results: The study included 184 infants with a mean gestational age of approximately 26 weeks. Daily fluid intake was consistent across gestational ages and various clinical parameters, including blood urea nitrogen (BUN), creatinine, and signs of diuresis. Correlations were noted between serum sodium levels and fluid intake on specific days. Infants diagnosed with a hemodynamically significant PDA received lower fluid volumes during the first two weeks. Percent weight loss by day 5 significantly correlated with lower rates of BPD and PDA.

Conclusion: Fluid intake was uniformly prescribed across our cohort, irrespective of hydration markers. Early weight loss in the first five days of life appears to influence morbidity, suggesting a need for personalized fluid management strategies in extremely premature infants.

Keywords: Neonatal Fluid Balance; Early Volume Status; Neonatal Fluid Overload; Neonatal Weight Loss

Abbreviation: NICU: Neonatal Intensive Care Unit; BPD: Bronchopulmonary Dysplasia; NEC : Necrotizing Enterocolitis; NEC: Necrotizing Enterocolitis; IVH: Intraventricular Hemorrhage; BUN: Blood Urea Nitrogen

Introduction

Fluid and electrolyte management is essential in the care of critically ill neonates but presents a unique challenge for clinicians. Premature infants are susceptible to fluid and electrolyte imbalances from postnatal changes in body water compartments, immature kidneys that inefficiently respond to fluid and electrolytes and increased insensible water losses across the skin and respiratory tract [1]. Extreme fluid and electrolyte dysfunction may be associated with increased morbidity and mortality, including bronchopulmonary dysplasia (BPD), persistent patent ductus arteriosus (PDA) and necrotizing enterocolitis (NEC) [2-4]. However, when fluid restriction is prescribed, providers may inadvertently decrease the amount of nutrition, including sodium,

a neonate receives which could be detrimental to growth and neurodevelopmental outcomes [5-9].

The ideal fluid strategy for premature infants is unknown. Fluid balance is a continuum and may vary between patients, making application of standard total daily fluid guidelines challenging [10-12]. Clinicians often use physical exam, serum electrolytes, weight change, and urine output to determine individual fluid goals, but an absolute standard has not been established and practice variation exists. To address this dilemma, we first aimed to summarize the daily fluid intake trajectories and delineate variability in fluid intake between extremely premature patients born ≤28 weeks in our Level 3 neonatal intensive care unit (NICU). Next, we aimed to determine clinical variables that impact fluid management in extremely premature infants, mainly daily sodium, BUN and creatinine values. Then, we assessed how early fluid management impacts morbidities, including BPD, hemodynamically significant PDA, NEC development and mortality. We hypothesized that there would be limited variability in daily fluid intake among our cohort, as no guideline exists for extreme premature neonatal fluid management; we suspected this would result in close adherence to our institutional nutrition protocol for uniform daily fluid advancement. We also surmised those with increased daily fluid intake would have higher rates of BPD, PDA and NEC due to inappropriate fluid accumulation disrupting physiologic hemodynamics throughout the body.

Methods

Study Design

This is a retrospective observational study of premature infants with a gestational age of ≤28 weeks admitted to Christiana Care NICU, a large single center level 3 unit, from January 2017 to December 2019. Infants admitted after 24 hours of life were excluded. The Institutional Review Board of ChristianaCare approved this study. We have followed the STROBE guidelines for reporting our study aims and results11.

Data and Data Preparation

Demographic, clinical and outcome variables were collected from the electronic medical record. Demographic variables included birth weight, gestational age, sex, singleton or multiple birth and race. Clinical variables were tracked daily over the first 14 days of life and included total fluid intake (ml/kg/day), highest serum sodium (mEq/L), blood urea nitrogen (BUN, mg/dL) and serum creatinine (mg/dL), weight (grams) and urine output (ml/kg/hr). Intake and output measurements were calculated using birthweight for the first seven days of life.

Fluid management was determined at the discretion of the medical team. The outcome variables in this study included diagnosis of BPD, PDA, NEC and mortality. BPD was defined per the 2000 National Institute of Health consensus statement definition12. PDA was considered hemodynamically significant if documented in the discharge summary or problem list and confirmed on echocardiogram, as echocardiograms are not routinely performed in our unit unless there is high suspicion for a persistent, hemodynamically significant PDA that may require medical intervention. NEC was considered present if infant received bowel rest and targeted antibiotic treatment for >48 hours and the diagnosis was listed in the discharge summary.

Statistical Analysis

The demographic and baseline clinical characteristics of the infants were summarized using means (± standard deviation, SD) for continuous variable and count (percent) for categorical variables. We compared baseline characteristic differences in neonates with and without BPD, PDA, IVH and NEC using chi-squared or Fisher's exact test for categorical variables, as appropriate, and t-tests or Wilcoxon rank sum tests for continuous variables, as appropriate. We fit separate multivariable logistic regression models of BPD, PDA, NEC and mortality to estimate the adjusted effect of total fluid intake when factoring gestational age, gender, race, and antenatal steroid exposure.

We summarized fluid intake trajectories for the first 14 days of life to determine variability in fluid intake amongst our cohort. This was done using a latent growth model that analyzes longitudinal data and estimates changes over time. The model was fit using lavaan package in R, and the predicted trajectories were visualized using *ggplot2*. Next, we aimed to determine whether total fluid intake was influenced by daily sodium, BUN and creatinine using Pearson correlation coefficients. We plotted the scatter plot of total fluid intake against sodium, creatinine and BUN for each day of life then fitted separate linear regression models of total fluid intake as a function of sodium, creatinine and BUN value for each day of life. The resultant R-squared value represents the proportion of variability in the daily fluid intake explained by sodium, creatinine and BUN values. We used a boxplot model to determine the differences in percent weight loss on BPD, PDA and NEC development. To handle missing outcomes, we performed pairwise deletion, resulting in an available case analysis, where cases were excluded only if data were missing on a required value. All data manipulation and analysis were done using R.

Results

Characteristics of the Study Population

We identified 184 neonates who met the inclusion criteria within our study period. We excluded 15 neonates who died during the 14-day follow-up period and 1 infant for whom the survival data was missing, resulting in an analysis population of 168 (Figure 1). Our cohort was composed of primarily Black male infants with a mean gestational age of 26.1±1.5 weeks and mean birthweight of 875.7±232.2 grams (Table 1).

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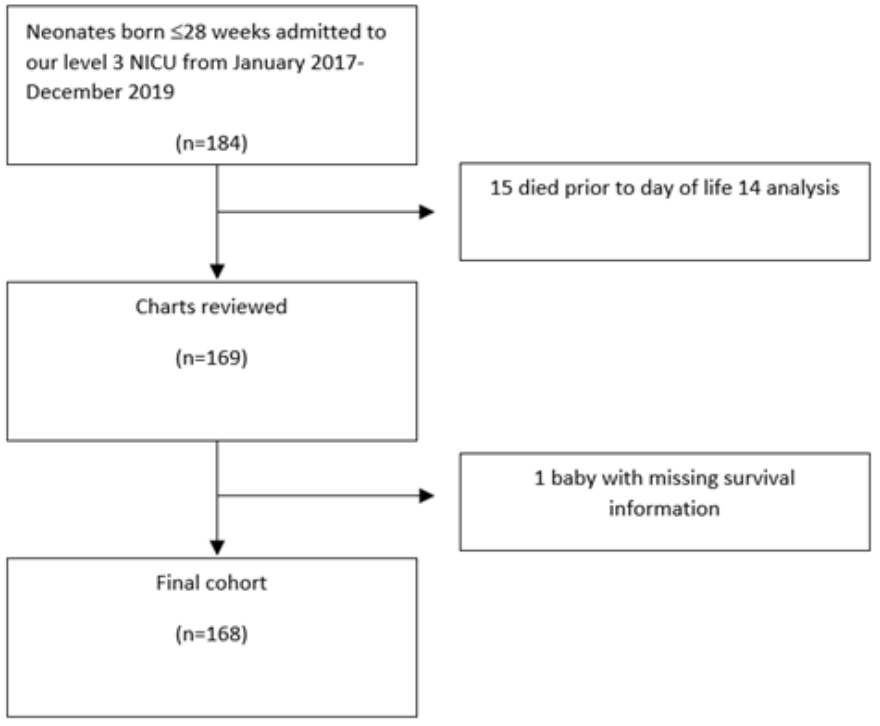

Figure 1: Shows our cohort included for data analysis.

Table 1: Summary of the patients' characteristics. The values are count and percentage unless otherwise mentioned.

	Overall
n	168
Sex %	
Female	81 (48.2)
Male	85 (50.6)
Race (%)	
Asian	8 (4.8)
Black or African American	98 (58.3)
Native Hawaiian or Other Pacific Islander	1 (0.6)
Unknown	5 (3.0)
white	56 (33.3)
Gestational Age weeks (mean (SD))	26.1 (1.5)
Birthweight (mean (SD))	875.7 (232.2)
Head Circumference at Birth (cm) (mean(SD))	23.6 (2.5)
Length at Birth (cm) (mean (SD))	33.7 (3.6)
Singleton Delivery (%)	
No	33 (19.6)
Yes	134 (79.8)
Antenatal Steroid Exposure (%)	
No	21 (12.5)

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Yes	145 (86.3)
Percent weight loss (mean (SD))	11.8 (5.8)
Percent weight loss from birth to DOL 5 (mean (SD))	8.2 (7.0)
Mean AFL (mean (SD))	134.2 (8.8)

A: Patients with and without BPD.

	BPD (n=94)	No BPD (n=58)	p
Female	43 (45.7)	31 (53.4)	0.505
Race (%)			
Asian	5 (5.3)	3 (5.2)	
Black	53 (56.4)	35 (60.3)	
white	36 (38.3)	15 (25.9)	
Not Hispanic or Latino (%)	86 (91.5)	56 (96.6)	0.376
Gestational Age Weeks (mean (SD))	25.6 (1.5)	27.0 (1.2)	<0.001
Birth Weight (mean (SD))	795.6 (207.8)	1010.2 (211.6)	<0.001
Head Circumference at Birth (mean (SD))	23.16 (2.7)	24.37 (2.1)	0.004
Length at Birth (mean (SD))	32.7 (3.6)	35.5 (3.0)	<0.001
Singleton Delivery	76 (81.0)	46 (79.3)	0.686
Antenatal Steroid Exposure	81 (86.2)	50 (86.2)	0.507
Weight loss (%mean (SD))	11.5 (5.9)	12.3 (5.1)	0.369
Weight loss percent from birth to DOL5 (mean (SD))	7.3 (7.6)	9.9 (5.4)	0.024
AFL (mean (SD))	134.3 (9.5)	134 (6.8)	0.91

B: Patients with and without hemodynamically significant PDA.

	PDA (n=82)	No PDA (n=72)	p
Female	39 (47.6)	39 (50.0)	0.377
Race (%)			
Asian	4 (4.9)	4 (5.1)	
Black	43 (52.4)	51 (65.4)	
white	33 (40.2)	19 (24.4)	
Not Hispanic or Latino (%)	74 (90.2)	75 (96.2)	0.244
Gestational Age Weeks (mean (SD))	25.4 (1.4)	26.9 (1.3)	<0.001
Birth Weight (mean (SD))	773.9 (177.7)	980.8 (235.2)	<0.001
Head Circumference at Birth (mean (SD))	23.1 (2.6)	24.1 (2.4)	0.01
Length at Birth (mean (SD))	32.4 (3.1)	35.1 (3.5)	<0.001
Singleton Delivery	65 (79.3)	63 (80.8)	0.543
Antenatal Steroid Exposure	70 (85.4)	68 (87.2)	0.381
Weight loss (%mean (SD))	11.1 (5.7)	12.3 (5.5)	0.173
Weight loss percent from birth to DOL5 (mean (SD))	6.7 (7.4)	9.7 (6.1)	0.006
AFL (mean (SD))	133.0 (8.7)	136.0 (8.0)	0.026

Variability of Fluid Intake in Our Cohort

Results from the latent growth model showed an average total fluid intake at day 0 of 218.3ml/kg with an estimated variance in slope of 3.9 ml/kg, indicating a higher variability of fluid intake on day 0 (Figure 2). This variability changed from day of life 1-14; day of life 1 data showed average expected total fluid intake was 138.7 ml/kg/day with an overall slope of 0.38ml/kg (Figure 2). This indicates, on average, fluid intake increases by 0.38ml/kg with each day of life over the first 14 days of life with little variance within the cohort. This data is clearly depicted in a box-scatter plot in Figure 2, showing greatest variability in fluid intake on day of life 0 and minimal variability in fluid intake on days of life 1-14 (Figure 3).

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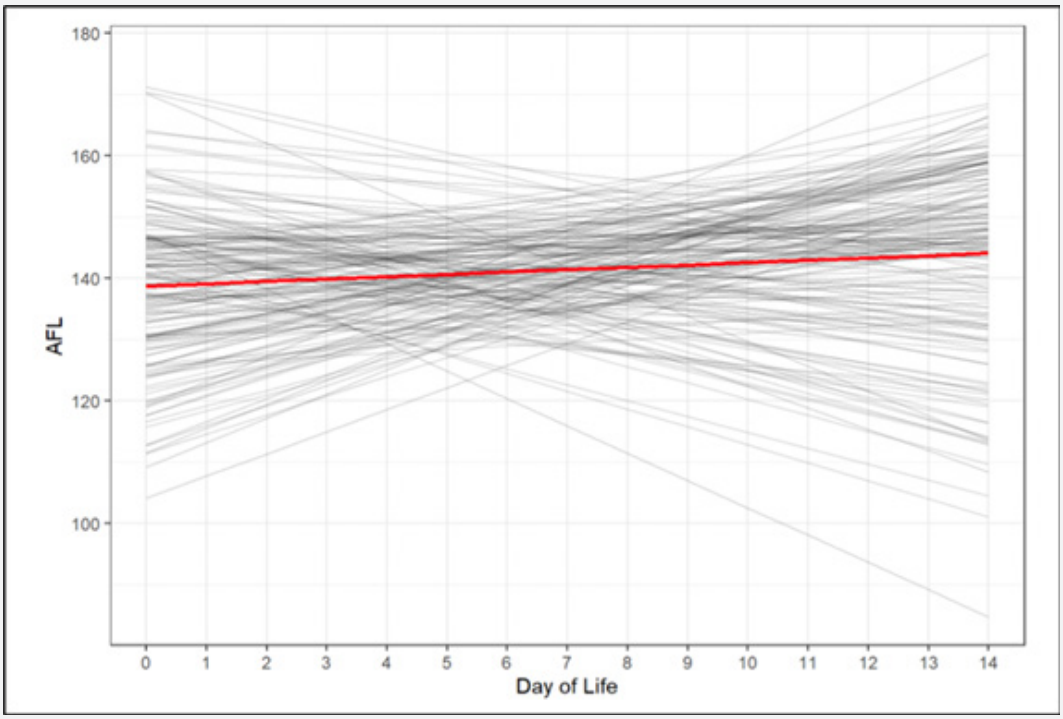

Figure 2: Trajectories of AFL in our population over the first 14 days of life.

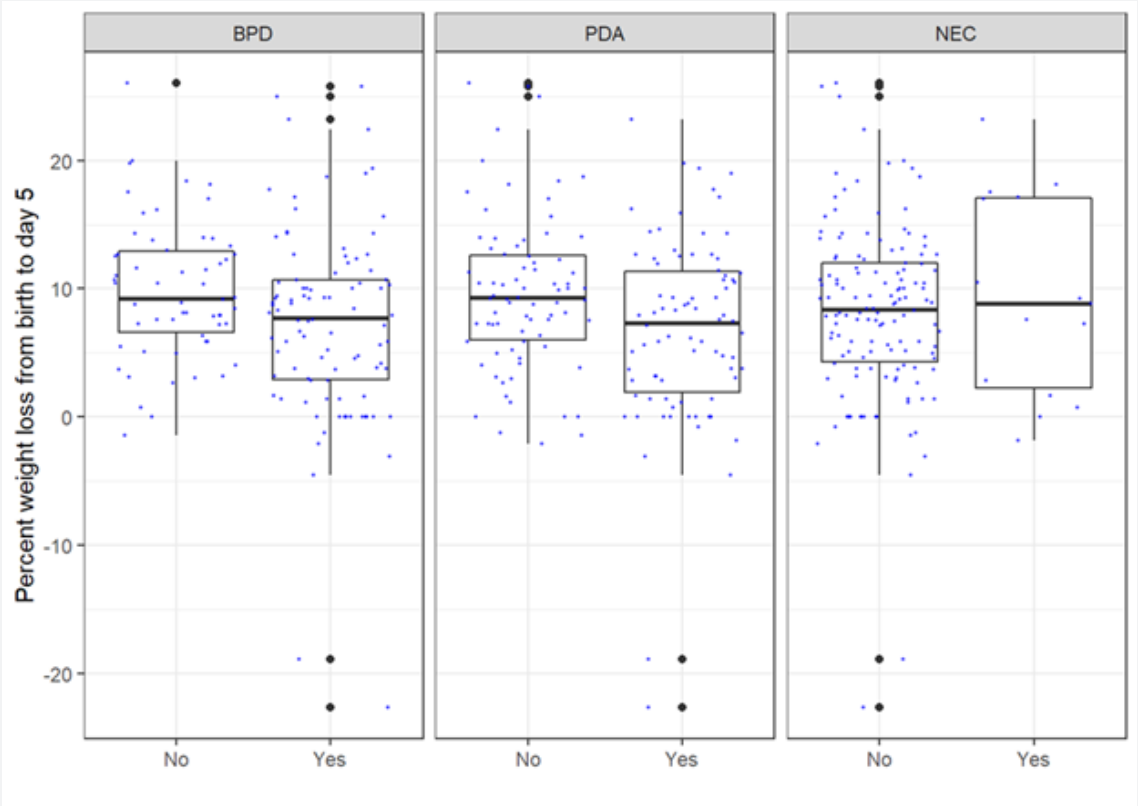

Figure 3: Impact of percent weight loss on BPD, PDA, and NEC. Percent weight loss was lower in those with BPD (p=.024) and PDA (p=0.006).

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Effect of Electrolytes on Fluid Intake

When investigating potential correlations between electrolyte concentrations and total fluid intake, we detected positive correlations between elevated sodium levels and increased fluid intake on DOL 0 (r=0.37, p<0.001), DOL 1 (r=0.49, p<0.001), DOL 2 (r=0.49, p<0.001), and DOL 5 (r=0.23, p=0.004). No correlation between daily maximum serum sodium and fluid intake was detected on the remainder of the analyzed days. We did not detect any correlations between serum BUN or creatinine and fluid intake on any DOL 0 through 14.

Effect of Fluid Intake on BPD, PDA, NEC and Mortality

Table 2 depicts baseline characteristics between those with and without BPD, PDA, and NEC. Sixteen neonates were excluded from the BPD analysis due to death or transfer prior to 36 weeks' gestation. BPD, PDA, and NEC were diagnosed in 52%, 52%, and 10% of patients, respectively. Average daily fluid intake was lower for patients with PDA (PDA: 133±8.7 ml/kg/day vs. no PDA: 136±8.0 ml/kg/day; p=0.03) compared to those without PDA, but average fluid intake did not differ between infants with and without BPD or NEC. There were no significant associations between fluid intake and mortality in our cohort.

Table 2: Comparison of the baseline characteristics between patients with and without BPD (A), PDA (B), and NEC (C).

	NEC (n=14)	No NEC(n=146)	p
Female	7 (50.0)	71 (48.6)	0.906
Race (%)			
Asian	2 (14.3)	6 (4.1)	
Black	7 (50.0)	87 (59.6)	
White	3 (21.4)	49 (33.6)	
Native Hawaiian or Other Pacific Islander	1 (7.1)	0 (0)	
Unknown	1 (7.1)	4 (2.7)	
Not Hispanic or Latino (%)	13 (92.9)	136 (93.2)	1
Gestational Age Weeks (mean (SD))	26.9 (1.33)	26.1 (1.6)	0.695
Birth Weight (mean (SD))	911.1 (271.4)	871.3 (228.2)	0.541
Head Circumference at Birth (mean (SD))	24.2 (3.4)	23.5 (2.4)	0.32
Length at Birth (mean (SD))	33.1 (4.2)	33.7 (3.5)	0.542
Singleton Delivery	11 (78.6)	117 (80.1)	0.936
Antenatal Steroid Exposure	12 (85.7)	126 (86.3)	0.891
Weigh loss (%mean (SD))	12.9 (6.1)	11.6 (5.6)	0.397
Weight loss percent from birth to DOL5 (mean (SD))	8.8 (7.8)	8.1 (6.8)	0.736
AFL (mean (SD))	133.5 (8.7)	134.5 (8.4)	0.66

C: Patients with and without NEC.

Effect of Weight Loss on BPD, PDA and NEC Development

We assessed the effect of post-natal weight loss on morbidity and found infants with less weight loss from birth to DOL 5 had greater rates of both BPD (BPD: 7.3±7.57% vs. no BPD: 9.91±5.39%; p=0.024) and hemodynamically significant PDA (PDA: 6.7±7.37% vs. No PDA: 9.7±6.07%, p=0.006) (Figure 3). The effect of weight loss on PDA was modified by gestational age; the odds of PDA decreased by 13% for each percent increase in weight loss for infants 27.1-28.9 weeks. This effect was not significant for infants born at a gestational age GA <27 weeks. Percent weight loss did not impact the diagnosis of NEC.

Discussion

Our cohort of neonates born ≤28 weeks had greatest variability in fluid intake on day of life zero, or day of birth. This accounts for both varying times of birth (i.e.: a baby born earlier in the day will have greater fluid intake than a baby born late in the evening) and different resuscitation requirements. However, there was minimal variability in fluid intake across our cohort from days of life 1-14, regardless of serum sodium, BUN, creatinine or percent weight loss. This suggests that adjustments in fluid intake did not reflect individual hydration and electrolyte needs in our population and that providers follow a similar fluid management plan for all extremely preterm infants. Perhaps a reason for this is the development of feeding advancement protocols which have become common practice in the NICU to guide enteral nutritional volume advancement to reduce the rate of NEC [13]. It is possible that some providers use the prescribed volume advancements in these protocols to guide fluid management in all patients. However, uncoupling fluid goals with clinical data used to assess fluid balance places preterm infants at risk for inappropriate fluid

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management and related complications.

Our data also showed insufficient weight loss in the first 5 days of life was associated with a diagnosis of PDA and BPD, adding to the growing literature that early fluid management impacts long term morbidity. Multiple studies have found increased risk of BPD in infants who received higher total fluid intakes [3,14,15] and less post-natal weight loss through the first 10 days of life [2,15]. Soullane et al evaluated the impact cumulative fluid balance, median serum sodium concentration and maximum percentage weight loss on death and/or BPD and found that only cumulative fluid balance was different between BPD-free survivors and infants with death/BPD [14]. In an adjusted analysis, there was an association between higher cumulative fluid balance and higher odds of death/BPD [14]. While our data did not show a difference in total fluid intake and BPD diagnosis, it showed a greater risk of BPD development with decreased post-natal weight loss in the first 5 days of life, highlighting that fluid balance is key to preventing BPD.

Additional studies have highlighted the importance of postnatal diuresis; a meta-analysis of 5 randomized controlled trials assessing the impact of liberal versus restricted fluid intake in premature infants demonstrated that increased postnatal weight loss significantly reduced the risk of significant PDA and NEC, while there were trends toward decreased risk of BPD, IVH and death [4]. Askoy et al demonstrated increased mortality for infants <1000 grams birth weight with weight loss of 0-3% from birth weight or greater than 12% [16]. Further, in a recently published secondary analysis of the PENUT trial, neonates with increased fluid balance were associated with increased odds of receiving mechanical ventilation on postnatal day 14, severe BPD, or death [15].

Our data supports the growing body of literature that the allowance of increased diuresis, defined by percent weight loss during the first week of life, may be a more important clinical variable to improve morbidity [2,3,13-15]. A recent quality improvement study by Havinga et al suggested that by simply decreasing starting fluid volumes, a goal weight loss of >6% of birthweight by the end of the first week of life can be accomplished [17]. This, in conjunction with our results, could warrant revision of the unit's fluid management protocol and allow for greater diuresis.

Limitations and Strengths

This study included a comprehensive collection of data regarding fluids goals in the first two weeks of life and clinical outcomes for a large group of extremely premature infants which contributes to its strength. However, many of the outcome variables are gestational age dependent, making it difficult to differentiate if the measured clinical variables, such as BPD and PDA of clinical concern, are due to degree of prematurity versus fluid status. Additionally, extremely premature infants are often not weighed daily, making actual fluid status and postnatal weight loss difficult to assess.

Since the clinical impact of the PDA and the need for treatment is controversial and without consensus, the relationship between fluid intake and impact on the PDA may have less clinical importance in patient management. Our study found a statistical but unlikely clinically significant difference in fluid intake for infants diagnosed with a PDA of clinical concern versus infants without a PDA. Additionally, there is practice variation for obtaining echocardiograms and treating hemodynamically stable PDAs, which could alter the number of patients who were diagnosed with PDA of clinical concern. Strict fluid management may have a greater impact on the PDA in certain groups within the extremely premature infant population. Infants <27 weeks are likely to be diagnosed with PDA regardless of fluid status but strict monitoring of percent weight loss and fluid infant for infants >27 weeks gestation may result in improved outcomes. Additionally, our unit does not routinely use humidity unless a neonate shows signs of refractory hypothermia despite thermal padding and heated isolette, which means insensible losses could have a larger impact than a unit who standardly uses humidity.

Conclusion

Fluid management in extremely premature infants is challenging. Our data revealed fluid intake was uniform across our cohort regardless of serum sodium, BUN or creatinine values or evidence of diuresis. This could be due to lack of guidance on extremely premature neonatal fluid management in conjunction with strict adherence to the unit's nutritional protocol which uniformly guides nutritional advancements without considering electrolyte balance or diuresis. Our study suggests that a higher percent weight loss within the first week of life is associated with a reduction in BPD and PDA diagnosis and thus should be considered an important variable for targeting fluid management.

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