Effect of Fluid Bolus on Clinical Outcomes in Very Low Birth Weight Infants

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OBJECTIVE Administration of fluid bolus in very low birth weight (VLBW) infants is a common practice in the NICU, but one without clear evidence demonstrating benefits in clinical outcomes. On the contrary, recent observational studies have suggested a potential detrimental effect of empiric fluid bolus in preterm infants, especially in the absence of clear indications. The aim of this study was to assess the impact of fluid bolus on various clinical outcomes in VLBW infants.

METHODS Retrospective cohort study of VLBW infants born at ≤ 34 weeks' gestation and/or ≤ 1500 -g birth weight at a single level III NICU from January 1, 2008, to December 31, 2013, and who received at least one fluid bolus within the first 48 hours of life. Outcomes studied were in-hospital mortality, need for home oxygen, incidence of chronic lung disease (CLD), prevalence of patent ductus arteriosus (PDA), and intraventricular hemorrhage (IVH).

RESULTS Of 516 infants, 112 (21.7%) received a fluid bolus within the first 48 hours of life for various indications. Propensity models suggested no statistical difference for CLD or mortality, but exposed infants had an increased incidence of home on oxygen ($p = 0.018$), PDA prevalence ($p = 0.008$), and IVH prevalence ($p = 0.038$).

CONCLUSIONS Fluid bolus in the first 48 hours of life may be associated with increased incidence of need for home oxygen and higher prevalence of PDA and IVH in VLBW infants. Future studies are needed to address these important adverse outcomes.

ABBREVIATIONS BP, blood pressure; BW, birth weight; CLD, chronic lung disease; GA, gestational age; IVH, intraventricular hemorrhage; MAP, mean arterial pressure; NICU, neonatal intensive care unit; PDA, patent ductus arteriosus; PIH, pregnancy-induced hypertension; VLBW, very low birth weight

KEYWORDS fluid bolus; intraventricular hemorrhage; IVH; patent ductus arteriosus; PDA; prematurity; VLBW infants

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Introduction

Early administration of fluid bolus in very low birth weight (VLBW) infants in the immediate neonatal period is a relatively common practice in the NICU¹ and is performed for varying indications, such as hypotension, poor perfusion, metabolic acidosis, and/or tachycardia in the neonate. It is estimated^{1,2} that up to 50% of extremely low birth weight infants may be perceived as having low blood pressure in the first few hours to days of life, and around half of them may receive some form of antihypotensive treatments.¹

Decisions regarding volume expansion in VLBW infants are complicated by lack of a validated or widely accepted definition of hypotension² as well as difficulty in assessing perfusion in the early neonatal period as a result of rapid, complex, and evolving physiologic changes in these infants as they transition from fetal to extrauterine life.³

Although fluid bolus is a common practice, there is

no clear evidence available to support the routine use of early volume expansion, and there is insufficient evidence demonstrating any benefit of volume expansion even with cardiovascular compromise.⁴ On the contrary, recent observational studies⁵ have suggested a potential detrimental effect of empiric fluid bolus in preterm infants, especially without clear indications. Human observational studies and animal studies have reported high prevalence of a pressure-passive cerebral circulation in critically ill preterm newborns and a strong correlation of both a pressure-passive state and hypotension with lower gestational age (GA) and birth weight (BW). These conditions places infants at risk for poor outcomes, including intraventricular hemorrhages (IVH).^{6–9} Additionally, liberal total fluid administration in the first few days of life may lead to an increased risk for persistent patent ductus arteriosus (PDA) in preterm neonates, which has been shown to be associated with worse respiratory outcomes in this population. Currently, no randomized control trial comparing the effect

of volume expansion on clinical outcomes for VLBW infants receiving fluid boluses (versus lack thereof) exists. Given this lack of evidence demonstrating clear benefits and concerns for potential harm associated with early fluid bolus, the objective of our study was to assess the effect of intravenous fluid bolus in the first 48 hours of life on mortality, respiratory, cardiac, and neurologic outcomes in VLBW infants born in our center. We hypothesized that VLBW infants who received fluid bolus within the first 48 hours of life had a higher likelihood of developing adverse outcomes compared to the infants who did not receive a fluid bolus.

Materials and Methods

This was a retrospective cohort study including all preterm infants ≤ 34 weeks of GA and/or a BW of ≤ 1500 g admitted to Baystate Medical Center's level III NICU from January 1, 2008, to December 31, 2013. This study received ethical approval by the Institutional Review Board at Baystate Medical Center, and informed consent was not required because of the retrospective nature of the study. We excluded any infant with known prenatal congenital, cardiac, or neurological anomalies.

Our exposure was defined as the administration of at least one 10 mL/kg of fluid bolus within the first 48 hours of life based on review of patient's electronic medical records. As the neonate needed to survive this 48-hour window in order for his exposure to be classified, we excluded all infants who did not survive the first 48 hours of life. We also collected information regarding the indication for the fluid bolus, type of fluid used, and duration of the fluid bolus administration. Additional data collected included patient's sex, mode of delivery, 5-minute Apgar score, and any significant maternal medical history. The initial outcome was the assessment of in-hospital mortality after 48 hours of life. Subsequent outcomes evaluated conditions at discharge, including development of chronic lung disease (CLD), discharge home on oxygen, prevalence of PDA, and IVH. Chronic lung disease was defined per the Vermont Oxford Network criteria as requirement of oxygen at 36 weeks corrected GA. The standard practice in our NICU is to start all premature infants at a total fluid goal of 80 to 100 mL/kg/day, with more premature infants more likely to start at the higher range of 100 mL/kg/day. The NICU has a small group of neonatologists, with similar practice styles guided by standard local protocols for PDA treatment, surfactant administration, and blood transfusion practices, which aids in uniformity of clinical practice.

For the study, *hypotension* was defined as a mean arterial pressure (MAP) lower than the GA of the infant, measured invasively through an umbilical artery catheter or measured non-invasively with a blood pressure cuff. Patent ductus arteriosus was diagnosed based on routine echocardiograms ordered by the supervising neonatologist based on clinical suspicion

during the NICU course of the infant, and for the study purposes, any sized ductus arteriosus (small, moderate, or large) was considered positive. Intraventricular hemorrhage was identified based on routine 1-week and/or 36-weeks corrected GA head ultrasound, and any grade IVH was considered positive.

We evaluated differences in subject characteristics across both the groups. Categorical variables are presented as frequencies and percentages, whereas continuous variables are presented as means and standard deviations. Unadjusted differences were estimated using logistic regression and reported as absolute differences and 95% CIs. To account for confounding we used 2 approaches: multivariable logistic regression (reporting adjusted absolute differences and 95% CI) and an inverse probability-weighted propensity score model (similarly reporting absolute differences termed *average treatment effects* and 95% CI). Both of these modeling approaches will adjust for group imbalances, although control of confounding is conditional on the measured covariates (we accounted for all covariates listed in Table 1). In addition, the propensity model attempts to address confounding by indication.¹⁰ For propensity models we assessed covariate balance and overlap assumptions. Covariates that remained unbalanced in the propensity model (weighted standardized differences of approximately >0.1) were added to the outcome model. Statistical significance was set at alpha of 0.05. In addition to these models, we conducted 2 sensitivity analyses using our propensity model approach. First, in an attempt to limit the influence of other indications for fluid bolus administration, we restricted our exposed sample to those with documented hypotension only. Second, we stratified the PDA and IVH outcomes by BW (<750 g vs ≥ 750 g). Analysis was conducted using Stata v15.1 (StataCorp, LP, College Station, TX).

With regard to power, we estimated the minimum detectable absolute difference in proportions assuming the least amount of power (baseline risk of 0.50) for all outcomes. In addition, we initially had a fixed sample size of 528 subjects; therefore, assuming an alpha of 0.05 and 80% power, we estimated that we could detect absolute differences of 15% across all outcomes assuming a 3:1 sampling ratio. As our observed baseline risk moves away from 0.50, power will increase, and we would be able to detect smaller absolute differences. However, we should note that power was limited when comparing GA stratifications; therefore, interpretation should be considered descriptive in nature.

Results

A total of 528 neonates were born at ≤ 34 weeks GA or weighing ≤ 1500 g during the study period. Twelve neonates who died within 48 hours of life (the exposure window) were excluded from the study. Of the remaining 516 neonates, 112 (21.7%) received a fluid bolus

Table 1. Baseline Demographic Information of Patients in Both Cohorts

Demographic Characteristics	Overall, N = 516	No Bolus Group, n = 404 (78.3%)	Fluid Bolus Group, n = 112 (21.7%)	p value*
BW, mean $\pm$ SD, g	1071.9 $\pm$ 298.1	1093.4 $\pm$ 286.2	994.4 $\pm$ 327.4	0.002
<750 g	92 $\pm$ 17.8%	62 $\pm$ 15.4%	30 $\pm$ 26.8%	
$\geq$ 750 g	424 $\pm$ 82.2%	342 $\pm$ 84.7%	82 $\pm$ 73.2%	
GA, n (%), wk				0.017
22–27	212 (41.1)	155 (38.4)	57 (50.9)	
28–34	304 (58.9)	249 (61.6)	55 (49.1)	
GA, median (IQR), wk	28.0 (26, 30)	29.0 (26, 31)	27.0 (25, 30)	<0.001
GA, n (%), wk				
22	1 (0.2)	0 (0.0)	1 (0.2)	
23	13 (3.2)	6 (5.4)	19 (3.7)	
24	20 (5.0)	17 (15.2)	37 (7.2)	
25	28 (6.9)	14 (12.5)	42 (8.1)	
26	43 (10.6)	12 (10.7)	55 (10.7)	
27	50 (12.4)	8 (7.1)	58 (11.2)	
28	45 (11.1)	10 (8.9)	55 (10.7)	
29	42 (10.4)	16 (14.3)	58 (11.2)	
30	58 (14.4)	10 (8.9)	68 (13.2)	
31	37 (9.2)	8 (7.1)	45 (8.7)	
32	34 (8.4)	7 (6.3)	41 (7.9)	
33	20 (5.0)	3 (2.7)	23 (4.5)	
34	13 (3.2)	1 (0.9)	14 (2.7)	
Female, n (%)	254 (49.2)	201 (49.8)	53 (47.3)	0.649
Cesarean delivery, n (%)	350 (67.8)	271 (67.1)	79 (70.5)	0.488
5-minute Apgar <7 [†] , n (%)	151 (29.5)	98 (24.4)	53 (48.2)	<0.001
Maternal history, n (%)				
PIH, n (%)	103 (20.0)	81 (20.0)	22 (19.6)	0.924
PPROM, n (%)	81 (15.7)	70 (17.3)	11 (9.8)	0.053
Chorioamnionitis, n (%)	20 (3.9)	15 (3.7)	5 (4.5)	0.715
Prenatal steroids, n (%)	368 (71.3)	295 (73.0)	73 (65.2)	0.104
End diastolic flow, n (%)	26 (5.0)	22 (5.4)	4 (3.6)	0.422

IQR, Interquartile interval (25th to 75th percentile); PIH, pregnancy-induced hypertension; PPRM, preterm premature rupture of membranes

* Unpaired t-tests for continuous outcomes, chi-square test for categorical outcomes.

[†] Missing data on 4 subjects.

within the first 48 hours of life, whereas 404 (78.3%) did not. Out of the 112 who received fluid boluses, 77 (69%) received the bolus within 1 hour of birth, and only one received the bolus at >24 hours of life (at 38 hours). The fluid bolus always consisted of crystalloid fluid, normal saline 10 mL/kg volume given intravenously over 30 minutes or 60 minutes. The most common indication for fluid bolus was hypotension (73%; n = 82), followed by poor perfusion (17%; n = 19), metabolic acidosis (8%; n = 9), sepsis (1%; n = 1), and hypovolemia (1%; n = 1).

Only 10 patients in the fluid bolus group who survived for >48 hours had persistent hypotension requiring further vasopressor treatment. Neonates in the fluid bolus group had lower BW, lower GA, and lower 5-minute Apgar scores compared to infants who did not receive a fluid bolus (Table 1). Median (interquartile interval) GA was 29 (26–31) weeks for those not receiving a bolus compared to 27 (25–30) weeks for those who did receive a fluid bolus. Mothers of neonates receiving a fluid bolus had lower rates of preterm premature rupture of

membrane and a slightly lower rate of antenatal steroid administration (Table 1).

We observed an overall mortality rate of 3.7% ($n = 19$) during the hospital course (Table 2). Initially, we observed a trend in increased mortality in neonates who received a bolus (fluid bolus: 6.3% vs no bolus: 3.0%, $p = 0.111$); however, after adjustment (both multivariable and propensity models) we found no clinical or statistical association between fluid bolus and mortality (absolute difference = -0.2% and 0.0% , respectively). These 19 deceased neonates were then excluded, and we assessed the remaining outcomes at discharge.

The unadjusted incidence of CLD was nearly 18% higher in the fluid bolus group compared with the no bolus group (fluid bolus: 60.0% vs no bolus: 42.3%, $p = 0.001$). However, in both adjusted models the risk difference was found to be closer to 5%, and this difference was no longer statistically significant. The unadjusted rates of need for home oxygen were almost 23% higher in the fluid bolus group (fluid bolus: 58.1% vs no bolus: 35.2%, $p < 0.001$); however, both adjusted models showed a moderation in this risk, with a statistically significant 12% increase in risk of need for home oxygen in the fluid bolus group (fluid bolus: 57.3% vs no bolus: 35.1%, $p = 0.018$) (Table 2).

In evaluating the association of fluid bolus with other pertinent clinical outcomes such as prevalent PDA and IVH, we observed a statistically significant increase in unadjusted associations. There was a 22% higher prevalence of PDA and a 14% higher prevalence of IVH in the fluid bolus group (fluid bolus: 47.6% vs no bolus: 25.8%, $p < 0.001$) and IVH (fluid bolus: 43.8% vs no bolus: 30.1%, $p = 0.008$). After adjustment, these associations were moderated but remained statistically significant, suggesting a 13% higher prevalence of PDA and a 12% higher prevalence of IVH in the fluid bolus group (PDA, propensity model: absolute risk difference = 13.1%, $p = 0.008$; IVH propensity model: absolute risk difference 11.8%, $p = 0.038$).

Our standard practice is to provide prophylactic indomethacin to all neonates weighing <750 g, which could potentially confound the outcome of PDA and IVH. Our multivariable and propensity models were already adjusted for birth weight; however, we also stratified our propensity models for IVH and PDA by neonates born at <750 g vs those born at ≥ 750 g. For PDA, we found that our estimate of the treatment effect for those born at ≤ 750 g was smaller than our overall estimate (9.1% vs 13.1%); however, the 95% CI for this estimate was wide, and statistical significance was lost, likely as the result of a smaller sample ($n = 78$, absolute risk difference = 9.1%, CI: -9.0 to 27.2, $p = 0.326$). For infants weighing ≥ 750 g, the model showed similar results to the overall estimates (absolute risk difference = 14.9%, CI: 4.6 to 25.2, $p = 0.005$). Estimates for IVH were similar for those born at <750 g, although statistical significance was again lost because of the smaller

sample (<750 g: absolute risk difference = 13.1%, CI: -11.0 to 37.3, $p = 0.286$; ≥ 750 g: absolute risk difference = 13.1%, CI: 0.7 to 25.6, $p = 0.039$). Because vasopressor use and resultant elevated blood pressures may also be associated with IVH, in another model we excluded subjects who had received vasopressors after the fluid bolus within 48 hours of life ($n = 10$) and excluded them from our IVH propensity score analysis; we then found the point estimate, 95% CI, and p values to be quite similar (absolute risk difference = 12.1%, CI: 0.5 to 23.8, $p = 0.041$) (Table 2).

One concern was possible noise contributed by neonates with other indications for a fluid bolus. In order to isolate our estimates we restricted our fluid bolus group to only those with documented hypotension and we compared those results with those of our full sample propensity models. Mortality estimates were marginally higher (increased from 0% to nearly 1%); CLD estimates were reduced from nearly 5% to 0%. Need for home oxygen risk was reduced from 12% to nearly 9%. Prevalent PDA was reduced from 13% to nearly 9%, and prevalent IVH was marginally higher (increased from nearly 12% to 13%) (Table 2).

Discussion

The most common indication for fluid bolus in our cohort was hypotension. Preterm infants undergo rapidly evolving complex physiologic changes in the immediate neonatal period, making it very difficult to identify an acceptable MAP range in this time frame¹¹; hence, there is no widely accepted definition of hypotension in this population.¹² Consequently, management of hypotension is highly variable in the immediate postnatal period.^{3,13} The most common approach is to give fluid boluses followed by vasopressor agents such as dopamine.¹⁴ It is uncertain whether hypotension itself results in adverse clinical outcomes such as IVH¹⁵ or adverse long-term neurodevelopmental outcomes.^{16–18} Results from one large neonatal database¹⁹ indicated that treatment of hypotension was associated with an increase in serious brain injury, which remained significant even after the mean was included in the regression model; therefore, it might be the treatment of hypotension itself that is harmful, rather than the presence of hypotension.¹⁹ Some studies^{20,21} in preterm infants with isolated hypotension have reported no change in cerebral tissue oxygenation with volume expansion and/or additional dopamine treatment, questioning the need for antihypotensive therapy in patients with isolated hypotension. Recently the practice of 'permissive hypotension,' which involves careful observation of hypotensive infants without signs of poor perfusion with therapeutic abstinence, has gained popularity.^{12,22} This seems prudent, as there is insufficient evidence to determine whether infants with cardiovascular compromise benefit from volume expansion,⁴ and with the potential risks associated with treatment, careful moni-

Table 2. Risk Differences Between the Fluid Bolus and No Bolus Group for Mortality, CLD, Discharge Home on Oxygen, PDA, and IVH

	No Bolus Group, n/Total (%)	Fluid Bolus Group, n/Total (%)	Absolute Difference*, % (95% CI)	p value
Mortality (incidence)				
Unadjusted	12/404 (3.0)	7/112 (6.3)	3.3 (−1.5 to 8.1)	0.111
Adjusted [†]	12/402 (3.0)	7/110 (6.4)	−0.2 (−3.4 to 3.0)	0.919
Propensity [‡]	12/402 (3.0)	7/110 (6.4)	0.0 (−3.1 to 3.1)	0.982
Restricted to hypotension§	12/402 (3.0)	7/80 (8.8)	0.8 (−2.7 to 4.2)	0.664
Chronic lung (incidence)				
Unadjusted	166/392 (42.3)	63/105 (60.0)	17.7 (7.1 to 28.1)	0.001
Adjusted [†]	165/390 (42.3)	61/103 (59.2)	4.8 (−3.4 to 13.0)	0.243
Propensity [‡]	165/390 (42.3)	61/103 (59.2)	5.3 (−3.6 to 14.3)	0.243
Restricted to hypotension§	165/390 (42.3)	46/73 (63.0)	0.0 (−9.7 to 9.6)	0.993
Home on oxygen (incidence)				
Unadjusted	138/392 (35.2)	61/105 (58.1)	22.9 (12.3 to 33.5)	<0.001
Adjusted [†]	137/390 (35.1)	59/103 (57.3)	12.4 (3.3 to 21.6)	0.007
Propensity [‡]	137/390 (35.1)	59/103 (57.3)	12.0 (2.0 to 21.9)	0.018
Restricted to hypotension§	137/390 (35.1)	45/73 (61.6)	8.8 (−1.8 to 19.4)	0.104
PDA (prevalence)				
Unadjusted	101/392 (25.8)	50/105 (47.6)	21.9 (11.4 to 32.3)	<0.001
Adjusted [†]	101/390 (25.9)	48/103 (46.6)	11.0 (2.0 to 20.1)	0.013
Propensity [‡]	101/390 (25.9)	48/103 (46.6)	13.1 (3.4 to 22.9)	0.008
Restricted to hypotension§	101/390 (25.9)	37/73 (50.7)	8.5 (−1.1 to 18.2)	0.082
BW <750 g¶			9.1 (−9.0 to 27.2)	0.326
BW ≥750 g#			14.9 (4.6 to 25.2)	0.005
IVH (prevalence)				
Unadjusted	118/392 (30.1)	46/105 (43.8)	13.7 (3.2 to 24.2)	0.008
Adjusted [†]	118/390 (30.3)	45/103 (43.7)	10.1 (−0.4 to 20.5)	0.051
Propensity [‡]	118/390 (30.3)	45/103 (43.7)	11.8 (0.6 to 22.9)	0.038
Restricted to hypotension§	118/390 (30.1)	34/73 (43.8)	13.0 (0.2 to 25.8)	0.046
Excluding vasopressors within 48 hr**			12.1 (0.5 to 23.8)	0.041
BW <750 g¶			13.1 (−11.0 to 37.3)	0.286
BW ≥750 g#			13.1 (0.7 to 25.6)	0.039

* No bolus = referent.

[†] Multivariable logistic regression controlling for age, BW, sex, delivery type, 5-minute Apgar <7, and maternal history variables. Chorioamnionitis not controlled for in mortality models as a result of collinearity.[‡] Propensity score model estimating average treatment effects using augmented inverse probability weighting.

§ Propensity model restricting exposure to those with an indication for hypotension.

¶ Propensity model stratified by BW <750 g vs ≥750 g.

** Propensity model excluding vasopressor use within 48 hr of life.

toring appears reasonable. In our study, of all infants who received fluid bolus in the first 48 hours of life, only 10 patients had persistent hypotension requiring further vasopressor treatment, suggesting that hypotension in most of the patients may have been transient and self-resolving, and hypotension treatment with fluid bolus

may not have been indicated if permissive hypotension was accepted. However, permissive hypotension also needs careful consideration, as one recent study²³ reported antihypotensive therapy to be associated with higher survival and lower rate of cerebral lesions than is permissive hypotension in extremely low birth weight

infants with early isolated hypotension.

In our study we demonstrated a possible association between fluid boluses within the first 48 hours of life and an increased risk of adverse outcomes, specifically discharge home on oxygen and the prevalence of PDA and IVH in VLBW infants. These results were in line with those of previous studies^{8,24–28} that demonstrated an increased association of adverse outcomes like IVH, PDA, and CLD with fluid boluses. Prior studies^{27–29} evaluating the relationship between fluid administration and CLD reported that infants with CLD were more likely to have received higher amounts of total fluids per kilogram within the first 4 days of life compared to their age-matched controls. These results indicated that postnatal administration of fluids may play an important role in the pathogenesis of CLD.²⁹ In addition, VLBW infants who received higher fluid amounts between the second and fourth days of life were more likely to develop CLD as compared with infants who received less total fluid.³⁰ Our data were consistent with these studies, suggesting that fluid bolus within the first 48 hours can be associated with increased pulmonary morbidities, hence the increased need for home oxygen.

In addition, studies^{24–26,31} evaluating fluid management in preterm infants have hypothesized that liberal fluid administration may interfere with PDA closure, with the potential for short- and long-term morbidities and the need for medical/surgical treatment of PDA. We also demonstrated a higher prevalence of PDA in fluid bolus exposed infants, even after adjusting for clinical parameters that were known to affect spontaneous PDA closure rates, such as GA and BW.³² We also found an increased prevalence of any IVH in the fluid bolus group. Although the highest rates of neurocognitive deficits have been reported with higher grades of IVH (III and IV), we chose to assess for any IVH because newer data suggested that even lower grades of IVH (I and II) could be independently associated with neurosensory impairment.³³ The lack of cerebral blood flow autoregulation along with the presence of highly vascular germinal matrix make preterm infants susceptible to IVH.³⁴ Any perturbations in hemodynamics can only augment this susceptibility, and although we cannot temporally place fluid administration prior to IVH onset, we should consider that efforts should be made to minimize unwarranted exposures such as empiric fluid bolus in the absence of evidence of known volume loss.

Our study was limited by its retrospective data collection process within a single center from 2008 to 2013. Although there have been no direct practice changes in hypotension and fluid bolus management since that time period, the outcomes may have differed over time. As a result of the retrospective study design we can only infer an association between fluid bolus and the adverse outcomes, and we cannot demonstrate causality. In addition, we were unable to determine which BP recordings reported in the electronic medi-

cal record were invasively measured (via a central line) and which were non-invasively measured (via a blood pressure cuff) because both are documented the same way in our electronic medical record. Also, because the secondary outcomes were assessed at the time of discharge, we excluded the infants who expired prior to discharge; the expired infants could not be assessed for CLD at 36 weeks or home oxygen at discharge, and only a few got head ultrasounds or echocardiograms prior to being deceased. Because there was no statistical difference in mortality between the 2 groups, we felt this approach would be appropriate in evaluating the data. The strengths of the study were that the clinical practice for fluid management was consistent among the practitioners, with detailed documentation of indication for any type of fluid boluses. The practicing physicians are a small group of neonatologists, with similar practice styles guided by standard local protocols for PDA treatment, surfactant administration, and blood transfusion practices. We also had a fairly large sample size, adding more statistical power to this study, compared with those of some other studies.

Although we used multivariate and propensity models to address confounding factors, the biggest limitation was confounding by indication, for which we were not able to fully account. In other words, sicker neonates might have received a fluid bolus, and the observed outcomes were due to the severity of their condition, not the fluid bolus. If future studies were either able to randomize neonates or if cohort studies were able to collect an indicator of endogenous vulnerability, such as Score of Neonatal Acute Physiology³⁵ or Clinical Risk Index of Babies³⁶ scores, we could either remove or better account for the influence of underlying illness severity and the resulting confounding by indication. We assessed for any PDA for the study, and we acknowledge that all-sized PDA might not be clinically significant. However, because this was a retrospective study, we were limited by wide variability in the timing of evaluation and treatment of PDA by the clinician; hence, we only evaluated for any PDA. We did evaluate for association of fluid bolus with any IVH, but it would also be beneficial in future studies to assess long-term neurodevelopmental outcomes in these premature infants.

Conclusions

In conclusion, we report an increased association of adverse outcomes such as discharge home on oxygen, PDA, and IVH, with exposure to fluid bolus within the first 48 hours of life in VLBW infants. This study further adds to the growing body of evidence that empiric fluid bolus may be more detrimental in the neonate when there is no clear evidence of fluid loss, and that permissive hypotension and close monitoring may be reasonable in scenarios without clear volume loss. Clinicians may need to be cautious about empiric fluid bolus

in preterm infants without clear indications for volume replacement. Future well-planned, large, randomized studies, with the potential use of near-infrared spectroscopy to evaluate for changes in cerebral perfusion with fluid boluses, are needed to evaluate the practice of fluid bolus in VLBW infants.

ARTICLE INFORMATION

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