A Paradigm Shift in the Risk Assessment of Intraventricular Hemorrhage in Relation to Intravenous Fluid Bolus in Extremely Premature Newborns within Seventy-Two Hours of Birth

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Abstract:

Objective:

To investigate the association of IV (intravenous) fluid bolus given within 72 hours of birth to premature neonates between 22 weeks to 28 weeks of gestation with the risk of development of IVH (intraventricular hemorrhage).

Methods:

A retrospective cohort study was done in a tertiary-level neonatal intensive care unit from January 2017 to December 2022. The infants included in this study were extremely premature neonates between 22 weeks to 28 weeks of gestation who received at least one 10 ml/kg of IV normal saline bolus within 72 hours of birth and had head ultrasounds within seven days of birth—classification of IVH used as per J. Volpe. SAS 9.4 version was used. Univariable analysis of categorical variables was performed with the chi-square or Fisher's exact test and for continuous variables, done with the student's t-test. Multivariable logistic regression analysis was done to identify the predictors of IVH.

Results:

One hundred four infants were included in this study. Birthweight, gestational age, vasopressor use in the first 72 hours of life, and pH were significant (p=0.017, p=0.032, p=0.040, p=0.0027, respectively) (Table 1). Fluid bolus was not significant on univariable analysis (OR 1.8, 95%CI 0.345–9.399, p=0.486); however, pH was significant (OR 20.78, 95% CI 2.293–188.435, p= 0.007). On multivariable logistic regression, patients with initial pH value <7.2 had 16.6 times the odds of grade 3 or 4 IVH compared to the patients with pH value ≥7.2 (aOR=16.63, 95%CI=1.46–189.01, p=0.02) after adjusting for baseline variables. The IV bolus on multivariable logistic regression was not significant (aOR=0.46, 95%CI=0.061–3.555, p=0.46).

Conclusion:

This study reveals that IV fluid bolus administration to extremely premature neonates within 72 hours of birth is not associated with an increased risk of IVH. However, caution should be exercised when interpreting the results as the sample size for higher grades of IVH was small, and further large prospective studies are needed to find a direct association between IV fluid bolus and the risk of development of IVH.

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Introduction:

IVH (intraventricular hemorrhage) is a common but significant complication that occurs in premature infants. Premature infants are at higher risk of developing IVH due to the presence of the germinal matrix. The germinal matrix is a highly metabolic region with a great degree of angiogenesis, most prominent at 23–24 weeks gestational age and less so by 28–32 weeks gestational age (**1**). Several factors contribute to the development of IVH in premature infants—including changes in cerebral blood flow and the lack of maturity to regulate this blood flow (2).

Administration of fluid bolus is common in NICU (Neonatal Intensive Care Unit), especially in premature infants, for resuscitation, metabolic acidosis, or hypotension. Hypotension is the most common indication for these extremely preterm infants to receive fluid bolus in the first few hours of life (3). Volume expansion to stabilize the cardiovascular system can increase vascular pressure in VLBW (very low birth weight) babies. Change in vasculature pressure is a risk factor for IVH (2). However,

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Bakshi et al. studied VLBW infants retrospectively to find associations between the administration of IV fluid bolus and adverse outcomes of prematurity (3). They found a higher incidence of oxygen requirement, patent ductus arteriosus (PDA), and IVH for the infants that received a bolus. Though the incidence was higher, there was no clinical significance (3). An animal study by Coulter et al. on premature rabbits looked at the IVH development after inducing a hypertensive environment by giving phenyl epinephrine and boluses (4). Their rabbit models failed to demonstrate any IVH in the premature rabbits after the insult.

Osborn et al. conducted a meta-analysis comparing currently available randomized controlled studies on the effects of early volume expansion in very preterm infants (5). One study by Beverley et al. included in this meta-analysis showed a significant reduction in periventricular and intraventricular hemorrhage (P/IVH) in preterm infants under 34 weeks gestational age who received fresh frozen plasma and those who did not. However, a similar study by Ekblad et al. failed to replicate these findings. A meta-analysis of these two studies also failed to demonstrate a significant difference in P/IVH between the treatment and control groups. (5)

Various predictors associated with the development of severe intraventricular hemorrhage have been identified in the literature, such as failure to receive antenatal steroids, male sex, 5 min Apgar score <7, intubation at birth, extremely low gestational age, transfer from another NICU (Neonatal Intensive Care Unit) and vaginal delivery. However, there is a paucity of evidence on the impact of intravenous (IV) fluid boluses as a risk factor for IVH in extremely premature neonates. NRP (Neonatal Resuscitation Program) in the current edition (8th) states that while giving fluid bolus for hypovolemia or hemodynamic instability, caution should be taken regarding the amount of bolus and administration time when given to infants <32 weeks gestational age (6).

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Currently, no human population studies have identified an association between early fluid bolus administration and IVH. We aim to look at preterm infants, primarily focusing on gestational age from 22–28 weeks, as there is a paucity of evidence on the association between the risk of IVH and bolus administration in this population in the first 72 hours.

Methods/Materials:

A retrospective cohort study was done in a tertiary-level neonatal intensive care unit (level 3 NICU) from January 2017 to December 2022. The infants included in this study were extremely premature neonates between 22 weeks to 28 weeks of gestation. We included infants who received at least one 10 ml/kg IV normal saline bolus within 72 hours of birth and had head ultrasounds within seven days. We excluded neonates who had any coagulopathy, NTD (neural tube defects), CDH (congenital diaphragmatic hernia), cyanotic CHD (congenital heart diseases), major structural anatomic deformity of head and trunk, death or transfer to a higher level of care within the first week of life. The institutional review board approved the study.

We collected data on infants and mother's demographic (infant

sex, infant race/ethnicity); birth weight as non-LBW (low birth weight), ELBW (extremely low birth weight) (<1000 g), VLBW (very low birth weight) (1000–1500g), LBW (<2500g); infant gestational age; mode of delivery; maternal medical history; prenatal care utilization; resuscitation (APGAR 1 min, APGAR 5 mins); inotrope use during resuscitation; required chest compressions; inotrope use in the first week of life (dopamine, dobutamine, epinephrine, norepinephrine, none); and ventilation details at birth and first blood gas parameters. The first blood gas collected was not restricted to arterial type, and all types (arterial, venous, and capillary) were considered, though priority was given to arterial blood gas if the infant had two or more types of blood gas at birth. Our institute restricts boluses to 10 ml/kg, provided over 30 minutes to 1 hour. We collected data for the number of boluses infants received within the first 72 hours and the reason documented for the bolus given. Our unit defined hypotension as mean arterial pressure (MAP) less than the gestational age. Metabolic acidosis necessitating bolus was taken as pH <7.2. Classification of IVH used as per Papillae (7). IVH was graded as no evidence of IVH; grades 1 and 2 IVH were favorable outcomes; and Grades 3 and 4 were unfavorable outcomes.

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Statistical Analysis:

All statistical analyses were performed using the weighted survey methods in SAS (version 9.4). Statistical significance was defined as p <0.05. Univariate analysis of differences between categorical variables was tested using the Chi-square test or Fisher's exact test, and continuous variables were tested using unpaired student's t-test. Multivariable survey logistic regression models were used to determine the odds ratio (OR) and 95% confidence interval for the association between intraventricular hemorrhage and intravenous fluid bolus in extremely premature newborns within seventy-two hours of birth. C-index (a measure of goodness of fit for binary outcomes in a logistic regression model) was calculated to assess the model's accuracy. A C-index of >0.6 was considered a good fit for the model. All statistical tests were 2-sided; p <0.05 was deemed statistically significant.

Results:

One hundred four infants were included in this study. Table 1 shows the baseline characteristics of the patient population. The mean gestational ages of the infants with no IVH, grade 1 or 2 and grades 3 or 4, were 26.3 weeks, 26.2, and 24.67 weeks of gestation, respectively. On univariate analysis, birthweight, gestational age, and vasopressor use in first 72 hours of life were significant (p=0.017, p=0.032, and p=0.040, respectively). We had a similar distribution of sexes (female N=50, male N=54).

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Table 1 also demonstrated the first gas parameters (pH, pCO2, base excess, and hematocrit) available at birth on admission to the NICU. pH value was categorized as <7.2 being acidotic and ≥7.2 as non-acidotic. pH was significant (p=0.0027). pCO_2 was used as continuous data with a mean of 42.94 (infants with no IVH), 50.56 (infants with grade 1 or 2 IVH), and 49.03 (infants with grade 3 or 4 IVH).

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Of the total infants in this study, 83 had no IVH, 15 had either grade 1 or 2 IVH, and six had Grade 3 or 4 IVH. Of the infants with no IVH, 52 (62.65%) did not receive IV fluid bolus, and 31 did (37.34%) [Table 1]. The neonates who weighed less had an

Table 1: Univariate analysis of demographic data, resuscitation, and hospital course in infants less than or equal to 28 weeks gestation, and diagnosis of IVH within first seven days of life.

|	No IVH N= 83, N (%) Mean (SD)	Grade 1 or 2 IVH N=15, N (%) Mean (SD)	Grade 3 or 4 IVH N= 6, N (%) Mean (SD)	P-value
Birth weight (g)	890.29 (268.49)	866.07 (235.78)	647.33 (158.51)	0.017
Gestational age	26.30 (1.65)	26.20 (1.32)	24.67 (1.21)	0.032
Sex				
Female	40 (48.2)	8 (53.3)	2 (33.33)	0.709
Male	43 (51.8)	7 (46.7)	4 (66.7)	
Mode of Delivery				
Vaginal	27 (32.5)	8 (53.3)	3 (50)	0.238
C-section	56 (67.5)	7 (46.7)	3 (50)	
Antenatal Steroids				
Yes	72 (86.7)	14 (93.3)	5 (83.3)	0.736
No	11 (13.3)	1 (6.7)	1 (16.7)	
Chest Compressions				
Yes	6 (7.2)	1 (6.7)	2 (33.3)	0.135
No	77 (92.8)	14 (93.3)	4 (66.7)	
Vasopressor use (during resuscitation)				
Yes	6 (6)	1 (6.7)	2 (33.3)	0.100
No	78 (94.0)	14 (93.3)	4 (66.7)	
Vasopressor use				
Yes	12 (64.5)	1 (6.7)	3 (50)	0.040
No	71 (85.5)	14 (93.3)	3 (50)	
Inborn/Outborn Delivery				
Inborn	65 (78.3)	11 (73.3)	4 (66.7)	0.758
Outborn	18 (21.7)	4 (26.7)	2 (33.3)	
APGAR at 1 min				
≤5	45 (55.6)	9 (60)	6 (100)	0.109
>5	36 (44.4)	6 (40)	0 (0)	
APGAR at 5 mins				
≤5	20 (24.7)	3 (20)	4 (66.7)	0.088
>5	61 (75.3)	12 (80)	2 (33.3)	
Blood gas parameters				
pH<7.2	15 (18.1)	4 (26.7)	5 (83.3)	0.0027
pH≥7.2	68 (81.9)	11 (73.3)	1 (16.7)	
pCO_2	42.94 (13.37)	50.56 (20.04)	49.03 (23.81)	0.3756
Base Excess				
≤ −5	49 (60.5)	12 (80)	5 (100)	0.1140
> −5	32 (39.5)	3 (20)	0 (0)	
Hematocrit	42.29 (8.27)	43.66 (9.65)	34 (8.54)	0.3402
Bolus administration in first 72 hours				
Yes	31 (37.35)	4 (26.67)	3 (50)	0.5386
No	52 (62.65)	11 (73.33)	3 (50)	
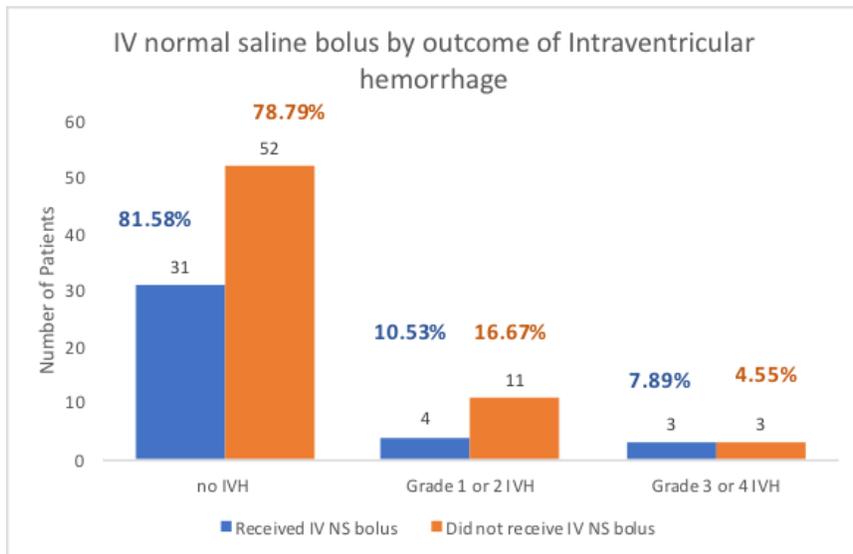
Figure 1: Percentages in the graphs are row%, which indicates the distribution of patients with Intravenous normal saline bolus and without bolus across different grades of IVH outcome.

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increased incidence of a higher degree of IVH, with the mean birth weights of the neonates with no IVH, grade 1 or 2 and grade 3 or 4 being 890.29 grams, 866.07 and 647.33 grams, respectively. Figure 1 shows the percentages in the graphs as row percentages, which indicates the distribution of patients with intravenous normal saline bolus and without bolus across different

> *"Intravenous fluid bolus was not significant on univariable analysis (OR 1.8, 95% CI 0.345–9.399, p=0.486) or on multivariable logistic regression analysis as well (aOR=0.46, 95%CI=0.061–3.555, p=0.46). On univariable analysis, pH was significant (OR 20.78, 95% CI 2.293–188.435, p= 0.007). On multivariable logistic regression, patients with initial pH value <7.2 had 16.6 times the odds of grade 3 or 4 IVH compared to the patients with pH value ≥7.2 (aOR=16.63, 95% CI=1.46–189.01, p=0.02)."*

grades of IVH outcome. 11 (16.67%) babies with Grade 1 or 2 IVH did not receive bolus, and 4 (10.53%) received a bolus. Three (7.89%) babies with grade 3 or 4 IVH received a bolus, and three (4.55%) did not.

Intravenous fluid bolus was not significant on univariable analysis (OR 1.8, 95% CI 0.345–9.399, p=0.486) (Table 1) or on multivariable logistic regression analysis as well (aOR=0.46, 95%CI=0.061–3.555, p=0.46). On univariable analysis, pH was significant (OR 20.78, 95% CI 2.293–188.435, p= 0.007) (Table 1). On multivariable logistic regression, patients with initial pH value <7.2 had 16.6 times the odds of grade 3 or 4 IVH compared to the patients with pH value ≥7.2 (aOR=16.63, 95% CI=1.46–189.01, p=0.02).

DISCUSSION:

This study is a retrospective cohort study carried out at a tertiary-level neonatal intensive care unit in the United States of America. We looked at six years of data from January 2017 to December 2022. Our sample size included 104 neonates between 22 and 28 weeks of gestation. Our study sample was significant for birth weight and gestational age (p=0.017 and p=0.032, respectively) to the risk of IVH, which is similarly reflected in current literature (p=0.04 and p=0.001, respectively) (8).

> *"Our study sample was significant for birth weight and gestational age (p=0.017 and p=0.032, respectively) to the risk of IVH, which is similarly reflected in current literature."*

A prospective study by Lee et al. (9) investigated a relationship between acidosis within one hour after birth and severe IVH defined as grades 3 or 4 and found a significant association (p<0.001). Szpecht et al. (10) conducted a retrospective study that examined the risk factors of severe IVH grades 3–4 in premature infants less than 32 WGA (p<0.0001). This study found significance between severe IVH and premature infants with acidosis who were

subsequently treated with sodium bicarbonate, though whether this significance was due to the acidosis or due to the treatment cannot be determined. Similarly, the effect of pH (p=0.027) on IVH was noted to be significant in our study. On multivariable logistic regression, patients with pH value <7.2 had 16.6 times the odds of grade 3 or 4 IVH compared to the patients with pH value ≥7.2 (aOR=16.63, 95% CI=1.46–189.01, p=0.02) after adjusting for baseline variables.

Synnes et al. (11) did a prospective data analysis from 17 NICU centers in Canada to further investigate risk factors of severe IVH. The significant risk factors reported from this study included Apgar scores at 5 minutes (Apgar <4, OR 2.1; Apgar 4–6, OR 1.5), outborn deliveries (OR 1.9), incomplete maternal antenatal steroid treatment (OR 0.6), and vasopressor use (OR 1.7). Our study found a significant association between vasopressor use and IVH (p=0.040). However, we did not see significance in Apgar scores at 1 minute (p=0.109) or 5 minutes (p=0.088) or a significant difference between outborn and inborn deliveries (p=0.758).

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An interesting finding in our data, which is contrary to previous literature (11), is that neonates who received antenatal steroids showed an increased incidence of IVH when stratified for various grades of IVH (antenatal steroids and grade 1 or 2 93.3% and grade 3 or 4 83.3% versus no antenatal steroids grade 1 or 2 6.7% and grade 3 or 4 16.7%). However, this was not numerically and statistically significant (p-value = 0.736).

Goddard et al. sought to develop an animal model for IVH by introducing a hypercarbic mixture through a ventilator rapidly in one group of beagle puppies and slowly in another group (12). Hypercarbia causes vasodilation of cerebral arteries and subsequently increases cerebral blood flow. 2 of the 9 total beagle puppies demonstrated histological features of IVH, and both had been exposed to rapid hypercarbia. Similar results were seen in another study by Johnson et al. (13). Although our study did not demonstrate statistical significance in pCO_2, the mean values were different between no IVH (42.94) and various grades of IVH (Grades 1–2 = 50.56, grades 3–4 = 49.03).

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Of the 104 neonates, 83 had no IVH, 15 had Grade 1 or 2 IVH, and only six had Grade 3 or 4 IVH. The worldwide incidence of intraventricular hemorrhage (IVH) ranges from 3.70 to 44.68%. The overall frequency of PIVH grades I, II, III, and IV in preterm infants is 17.0%, 12.1%, 3.3%, and 3.8%, respectively (14). When PIVH occurs, about 50% occur on the first day of life, and by the third day of life, it is 90% (14). Thus, the goal was to screen infants within the first week of life to capture most IVH occurrences. The sample size for grade 3 and 4 IVH was small (six patients: three who received bolus, and three did not); hence, the study's results should be interpreted cautiously due to this limitation.

IVH is related to significant long-term complications such as cerebral palsy and language, cognitive and motor delays, and comorbidities. A retrospective study by Aslam et al. showed a higher incidence of bronchopulmonary dysplasia in very preterm infants who received saline bolus within their first week of life compared to those who did not (15). The persistence of the germinal matrix puts premature neonates at greater risk of developing intraventricular hemorrhage. Additionally, their decreased capacity for cerebral autoregulation has warranted caution in situations that may cause sudden changes in cerebral blood flow. We hypothesize that the previously held idea of the impact of IV fluid on IVH in extremely premature newborns is likely an extrapolation of studies done on newborns of a broader range of gestations and birth weights, as we were not seeing an increased incidence of IVH with IV fluid boluses on our unit in extremely premature neonates. There is no statistical difference in the risk of occurrence of IVH if they receive fluid bolus or not (aOR=0.46, 95%CI=0.061–3.555, p=0.46).

One limitation of our study was a small sample size for grade 3 and 4 IVH (six patients, three who received bolus and three who did not). Additionally, the interpretation of the pCO_2 and O_2 data is limited as the first blood gas collected was not restricted to the arterial type. Due to the study's retrospective nature, there was probably a lack of control over exposure factors and other potentially confounding variables. We also did not compare our results with neonates who developed IVH and did not receive IV saline bolus. The study's results should be interpreted cautiously with these limitations in mind. Further prospective studies are needed to develop an association between the relationship between IVH and the administration of IV fluid boluses, but these are difficult to conduct due to ethical reasons.

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"This study reveals that IV fluid bolus administration to extremely premature neonates within 72 hours of birth is not associated with an increased risk of IVH. Our findings support prior retrospective studies and animal models, which similarly failed to show an association between early volume expansion and IVH in premature infants. We encourage diligence while administering IV fluid bolus to extremely preterm infants. Although randomized control trials might be a challenge to run on this subject, further multi-center prospective trials are required on this study population before the findings of this trial can be used in clinical practice."

This study reveals that IV fluid bolus administration to extremely premature neonates within 72 hours of birth is not associated with an increased risk of IVH. Our findings support prior retrospective studies and animal models, which similarly failed to show an association between early volume expansion and IVH in premature infants (9, 10, 11). We encourage diligence while administering IV fluid bolus to extremely preterm infants. Although randomized control trials might be a challenge to run on this subject, further multi-center prospective trials are required on this study population before the findings of this trial can be used in clinical practice.

Conclusion:

This study reveals that IV fluid bolus administration to extremely premature neonates within 72 hours of birth is not associated with an increased risk of IVH. However, caution should be exercised when interpreting the results as the sample size for higher grades of IVH was small, and further large prospective studies are needed to find a direct association between IV fluid bolus and the risk of development of IVH.

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