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Relationship between hypernatremia & Intra-ventricular hemorrhage in very & extremely preterm neonates

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Abstract

Background and Objectives

For identifying important risk factors that contribute to intra-ventricular hemorrhage (IVH) and hypernatremia in early postnatal life of preterm neonates of extremely low birth weight, with gestational age (GA) matching appropriately and with birth body weight (BBW)

Material and Methods

The study has been designed to evaluate extremely preterm neonates with GA ≤ 26 weeks and BBW ≤ 1000 g, admitted to different hospitals during the 8 years. The data has been collected every month from 1990-2019

Results

The regression results indicated a significant relationship between sodium serum level and IVH, hypernatremia in extremely preterm neonates. Hypernatremia and fluctuations are related to sodium that seems to be associated with early severe IVH among preterm neonates It is found that hypernatremia is a major risk factor for IVH in extremely preterm neonates. It is explored that the incidence of hypernatremia in extremely preterm neonates preterm neonates along with other contributing factors. It is recommended for future research to find other contributing factors to examine this research in further details.

Conclusion

There found some factors significantly affect resuscitation, vaginal delivery, hemoglobin, male sex, level of high sodium serum, fluctuation of serum sodium, and platelet counts are also associated within f severe IVH and hypernatremia. The study concludes, a significant positive relationship between hypernatremia & Intra-ventricular hemorrhage in very & extremely preterm neonates along with other contributing factors. However, further research is required to explore a causal relationship between IVH and hypernatremia in extremely preterm neonates.

Keywords: hypernatremia, Intra-ventricular, preterm neonates, resuscitation, serum sodium

Background

Intra-ventricular hemorrhage (IVH) is observed quite often neonatal morbidity among extraordinarily premature preterm neonates. It leads to adverse sequelae on the development of neurons. Therefore, during the last decade, the incidence has been declined but still, IVH is considered a highly significant risk factor for morbidity and mortality among extraordinarily premature preterm neonates. The literature revealed that approximately 90% of cases, IVH, have been occurred during first three days of postnatal. However, it is evident that the gestational age (GA), in this incident is inversely associated with birth body weight (BBW). Therefore may risk factors are associated with males related to IVH, as male gender, as membranes can be ruptured at a premature stage, delivery method, postnatal resuscitation, onset sepsis at a very early stage, hypoxemia, syndrome of respiratory distress, pneumothorax, hyper, and hypocarbia [1]. Furthe.rmore, it was reported that IVHs were observed to be very more common among preterm neonates with hypernatremia. The previous literature, therefore, explored insufficient evidence about the appropriate matching controls for BBW and GA, thus was simply investigated that the population carry high risk but the outcomes might be confounded by both the variables, However, the case-control study has been conducted to minimize the effects of GA and BBW as well as the potential risk factors have been determined for severe IVH. Intraventricular hemorrhage (IVH) is considered as the most important element that caused mortality along with the developmental impairment during long run in preterm neonates. The definite neurologic sequelae frequency is, therefore, directly concerned with the IVH severity. Chorioamnionitis (CA) is also a common risk factor in the disease of prematurity for the white matter, however, the association of intraventricular hemorrhage (IVH) to preterm neonates is still controversial and it is not yet systematically reviewed with empirical investigation. However, comprehensive literature is available that has been conducted by using PubMed/MEDLINE and EMBASE after 2017. This literature includes the investigation regarding preterm neonates. It is reported that the primary data has been used to measure the association between IVH, hypernatremia, and preterm neonates. It is found that in the previous literature the random-effects model was extensively used for odds ratios (OR) calculation at 95% confidence intervals. We have observed that 1,284 relevant studies have been found in literature, out of these 85 has met the inclusion criteria i-e 46,244 preterm neonates with 13,432 cases of hypernatremia [2]. The Meta-analysis was also conducted in literature and found a significant association between hypernatremia with all IVH grades and preterm neonates with CI 1.61–2.19 and OR 1.88, 95%, therefore, with 1–2 IVH grades at CI 1.22–2.34 and OR 1.69, 95%, and with 3–4 IVH grades at CI 1.42–1.85 and OR 1.62, 95. However, both histological CA and clinical were also significantly associated with increased risk in the development of IVH in extremely preterm neonates [3–5]. Contrary to this, the funisitis presence has not been increased IVH risk as compared to CA but in the absence of funisitis, CI 0.89–1.67 and OR 1.22, 95% was observed.[6] Moreover, this meta-analysis had confirmed the initial findings have exposed preterm neonates with CA have lower gestational age (GA 1.20 weeks) with the lower birth weight i-e BW; MD −55 g these preterm neonates not significantly exposed to CA. However, multiple regression analyses do not demonstrate proper association between the IVH and hypoxemia in lower GA and BW of the preterm infant [7]. The grade 1/2 IVH is compared with the neurosensory impairment at the highest, observed at almost doubled in number i-e severe-grade is grade 3/4 of IVH. According to the classification of Papile, severe grade IVH, as a critical incident, was estimated at the level of approximately 6 to 16%, whereas in the large cohort of preterm network of preterm neonates with birth weight < 1,500 g.it is an unfortunate incident to find severe IVH in extremely preterm neonates, however, the results are largely remained the same over a decade, though many efforts have been made for avoiding or minimizing the IVH perinatal risk factors. Many of previous research have proposed several IVH perinatal risk factors also including the following: gestational age (GA) low birth weight gender, absence of antenatal steroids, intrauterine infection, mode of delivery, hyper apnea, hypoxemia, pulmonary hemorrhage, respiratory distress syndrome (RDS), pneumothorax, bicarbonate infusion, and metabolic acidosis [8–12].

The IVH pathogenesis is multifactorial; it includes, broadly, the germinal fragility matrix vasculature, blood flow fluctuation in cerebral, and platelet and coagulation disturbances. However, the association between tracranial hemorrhage and hypernatremic dehydration has been well-defined among pediatric patients and newborn preterm neonates. However, it is uncertain that the early fluid change or level of serum sodium would affect the severe IVH occurrence in preterm neonates. Therefore, a few studies revealed a possible association between IVH and hypernatremia; it is also observed that the cause and effect relationship in high sodium intake and preterm neonates has remained unclear. The purpose of this study is to examine and investigate the association between severe IVH and concentration of serum sodium as well as the impact of sodium intake in the early days of extremely preterm with low birth weight preterm neonates [13–15].

Methodology

Objectives

- To explore hypernatremia as a risk factor for IVH in extremely preterm neonates
- To investigate the incidence of hypernatremia in extremely preterm neonates' preterm neonates along with other contributing factors.

Mathematical model and variables:

The relationship is examined by applying OLS regression with DV: Sodium Serum level in preterm neonates/neonates. IV: IVH (Intra-ventricular hemorrhage), Birth weight, Sex/ gender, the Sugar level of preterm neonates as a proxy of hypernatremia test excess water in the body.

Sodium Serum level in preterm neonates/neonates

$$= \alpha + \beta_1\ IVH + \beta_2\ BW + \beta_3 Sex + \beta_4\ SL + \beta_5\ HYP + €_t$$

Sodium Serum: Sodium: it is a vital source for muscle function and nerves. The body keeps balanced sodium with a variety of mechanisms. The Sodium level in preterm neonates is determined by food and drink of mother. However, high level of sodium cause increase in blood pressure resulted in Intra-ventricular hemorrhage of neonates [16]

Intra-ventricular hemorrhage: it is also describes as “intraventricular bleeding” bleeding into ventricular system of brain. Moreover, cerebrospinal fluid is produced as well as circulated through subarachnoid space and physical trauma has been observed as hemorrhaging in stroke. The important factors include: Fluctuation in flow of cerebral blood flow (related to blood pressure) , ↑ flow of cerebral blood due to hypercarbia, ↑ pressure of cerebral venous with pneumothorax and asphyxial heart failure, reperfusion and hypotension and coagulation abnormalities.

Birth weight: The average birth weight of babies is 3.5 kilograms (7.7 lb), it is also considered as normal to be between 2.5 kilograms (5.5 lb) and 4.5 kilograms (9.9 lb) in Europe , however, the research found it different in other countries [17].

Gender: many previous studies found that male neonates are more sensitive towards hypernatremia & Intra-ventricular hemorrhage [19].

Sugar level: the sugar level (very low or very high) leads to hypernatremia & Intra-ventricular hemorrhage in preterm neonates [20].

The output of the regression model will be discussed according to DV and IV , P value (<5%) along with the graphical representation done in SPSS [21–23].

This study is conducted in the "neonatal intensive care unit" (NICU), the data has been collected from the NICU databases of USA. These databases recorded the medical information of preterm neonates from admission till discharge from January 1990 to December 2019 of preterm neonates of a GA p26 weeks, having BBW p1000 g, and were diagnosed with IVH with both grades III and IV. The pediatric neurologist used to perform the Routine cranial ultrasound within first 3 days of life in the NICU. However, the grading of IVH has been made according to the system of Papile classification,7andgrades, grade III or IV, while it is defined that IVH is severe.[24–26] The preterm neonates with brain malformations are excluded from this study, moreover, the orcongenital anomalies of dysmorphic features have suggested the chromosomal abnormalities, metabolic disorders, and genetic syndromes. The study has been designed to evaluate extremely preterm neonates with GA ≤ 26 weeks and BBW ≤ 1000 g, admitted to different hospitals for 8 years. The data has been collected every month. The preterm neonates, the cohort of 347, out of these, 36 preterm neonates i-e 10.7% had suffered from severe IVH i-e grades III and IV. [27–29] We have selected the control group of preterm neonates (36) without IVH and hypernatremia, closely matched for the GA (± 1 week) with body weight (± 100 g). The effect of sodium serum intake for the extremely preterm neonates has been investigated. A regression analysis was applied to identify risk factors found in preterm neonates for severe IVH and hypernatremia. However, GA of IVH and hypernatremia was 24.6 ± 1 week with BW 764.4 ± 118.5 g, and 24.8 ± 0.9 weeks with 771.5 ± 125.9 g, respectively.

Considering (X1, Y1) both points near the upper right of the data collected. The observed value of an independent variable is X1(sodium serum) and the observed value is described as Y1, for IVH, BW, Sex, SL, HYP as dependent variables respectively. The regression line has been used to predict the dependent variable value, the value Y^1 has been predicted. These dependent variables were obtained by putting X1. X2, X3, X4, and X5 in the equation, and

$$Y\hat{}\,1 = a + bX1 + bX2 + bX3 + bX4 + bX5 \qquad (1)$$

The error of prediction for Sodium Serum level in preterm neonates/neonates is given by:

$$\alpha+\beta_1\ IVH+\beta_2\,BW+\beta_3 Sex+\beta_4\,SL+\beta_5\,HYP+€_t \qquad (2)$$

$$X1 \text{ is } Y1 - Y\hat{} \qquad (3)$$

By entering X1, in the given equation, the value of X, it is possible to make it close to the predicted value of sodium serum (dependent variable), however, there found some error in this prediction. The least-squares regression line has the aim to minimize the error of prediction. The error of prediction is associated with X1 as:

$$€1 = Y1 - Y\hat{} \qquad (4)$$

This point lies between X2 and Y2 with a considerable distance from the regression line is considered as a prediction of error.

$$Y2 - Y\hat{} \qquad (5)$$

When X = X2, the serum sodium's observed value, Y is Y2 then predicted value of

$$Y \text{ is } Y\hat{} = a + bX2 = Y\hat{} \qquad (6)$$

The error in predicting term is associated with

$$X2 \text{ is } e2 = Y2 - Y\hat{} \qquad (7)$$

A similar error term for prediction would be obtained from observation at different data points, so there could be several possible lines that could be drawn. All of these points have been associated with some set of errors to predict Y values. Moreover, these lines could be fitted with the points of the scatter diagram better than do other lines. Therefore, the better fitting lines contain the smaller errors for predicting the lines. However, one of the regression model objectives is to find the points on the line best fitted to all. To find the regression line, the statisticians usually used the least-squares criterion. This criterion contains certain attempts for minimizing the sum of the squares from the errors to predict. This minimization has produced the line to fit the best of all observed points. [30–33]

The least-squares criterion would be written in the algebraic form as: n observed points = (Xi, Yi),

where i = 1, 2, . . ., n.

Considering a line that has been drawn for each observed value of X, however, a predicted Y value = Yˆ has to be obtained by putting the value of X in the equation to the line. These predicted values of Y will differ from the observed values of Y. to each of the ith observation the difference found between observed and predicted value i-e written

ei = Yi − Yˆ i.

The criterion to determine the line fitted to the point best positive and negative errors that have been canceled out so X ei = 0.

The squares of error terms, e 2 i = (Yi − Yˆ i) 2, the sum of the squares of errors,

Xe 2 i = X (Yi − Yˆ i) 2

The line of least square regression is a straight line with minimum possible values of error for this sum. It can also be defined mathematically moreover, there is only one regression line to satisfy the criterion X ei = 0 , which has produced Minimum X= e 2 i. It is being shown that with algebra and calculus that this occurs when a and b found the values as:

$$a = \bar{Y} - b\bar{X}\ b = P\,(Xi - \bar{X})(Yi - \bar{Y})\ P(Xi - \bar{X}) \tag{8}$$

This intercept a and slope b are the statistics that produce the line that fits the points the best. All other possible lines result in larger values for the sums of the squares of the errors of prediction, P e 2 i. The values of a and b can be computed as shown in the above formulas, but computationally it is more straightforward to use the formulas that were developed when determining the correlation coefficient. In Section 11.4.3, the values SXX and SXY were used. These were defined as SXX = XX2 − (P X)2 n SXY = XXY − (P X)(P Y) n These expressions can be calculated from the observed values of X and Y in the same manner as in Section 11.4.3. Based on these expressions, the slope and intercept can be shown to equal

$$b = SXY\ SXX\ a = \bar{Y} - bX \tag{9}$$

Table 1 *Summary of Simple Regression Analyses for Variables Predicting: hypernatremia & Intra-ventricular hemorrhage in very & extremely preterm neonates (n = 24)*

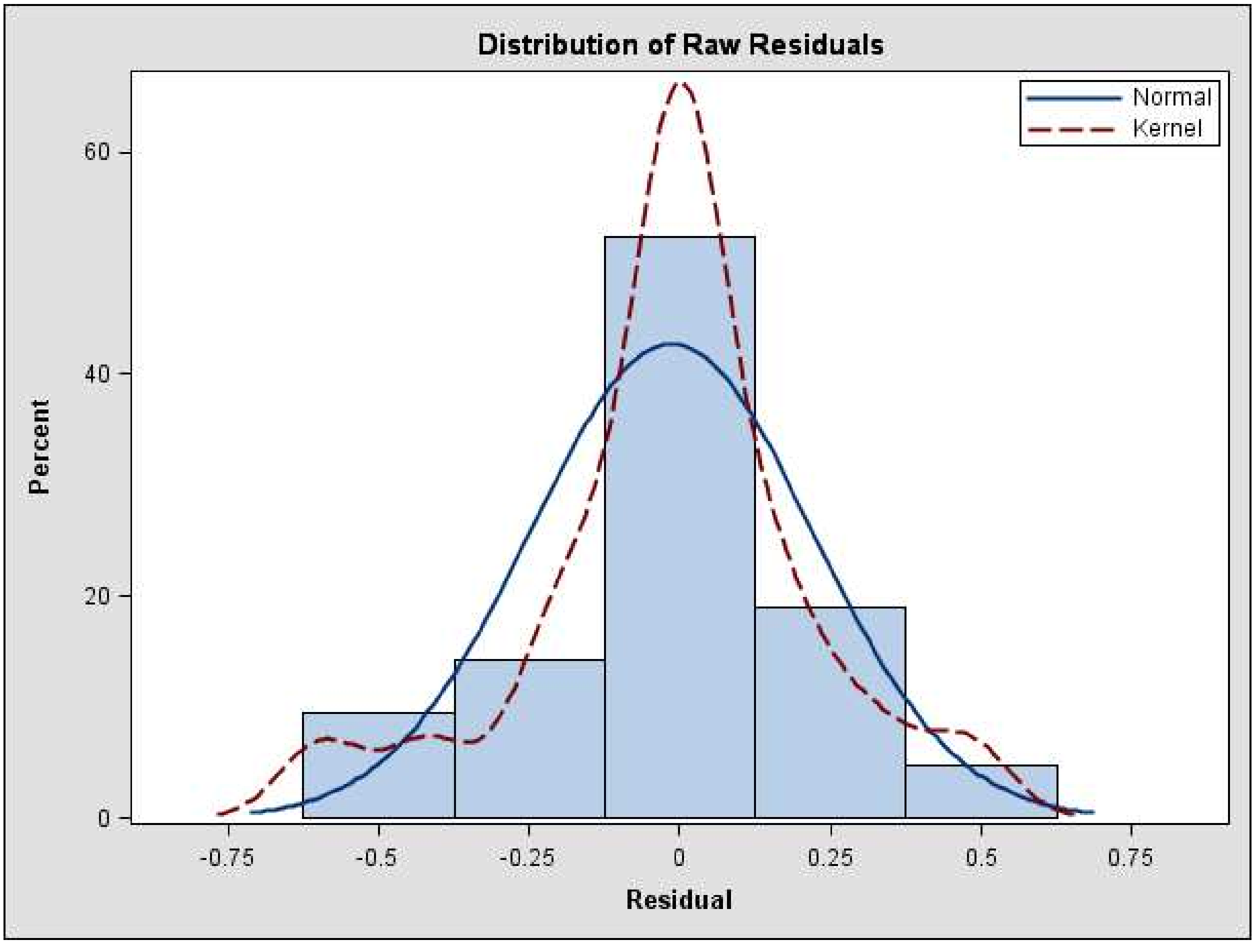
Variable	α	IVH	β	BW	B	Sex	β	SL	β prob.
Sodium serum	0.08	0.0546	0.625	0.0252	0.764	0.063	0.023	0.0533	0.754 0.01
Mode of Delivery	0.01	0.0643	0.162	0.0265	0.345	0.0564	0.643	0.0345	0.445 0.00
Hemoglobin fluctuations	0.02	0.0085	0.233	0.01514	0.543	0.0568	0.754	0.0424	0.865 0.00
Gestational age	0.1	0.097	0.821	0.01754	0.875	0.0854	0.054	0.0754	0.754 0.01
Respiratory issues	0.05	0.076	0.514	0.0161	0.446	0.0235	0.035	0.0981	0.045 0.00

Coefficients

Model		Unstandardized Coefficients		Standardized Coefficients	t	Sig.
		B	Std. Error	Beta		
1	(Constant)	16.807	2.934		5.727	.000
	Ss	1.143	.097	.731	11.773	.000

Table 2 Residuals Statistics

	Minimum	Maximum	Mean	Std. Deviation	N
Predicted Value	37.3721	68.2202	50.6179	7.13031	123
Residual	-15.93980	20.34524	.00000	6.66186	123
Std. Predicted Value	-1.858	2.469	.000	1.000	123
Std. Residual	-2.383	3.041	.000	.996	123



ANOVA

Model		Sum of Squares	Df	Mean Square	F	Sig.
1	Regression	6202.633	1	6202.633	138.615	.000[b]
	Residual	5414.408	121	44.747		
	Total	11617.041	122			

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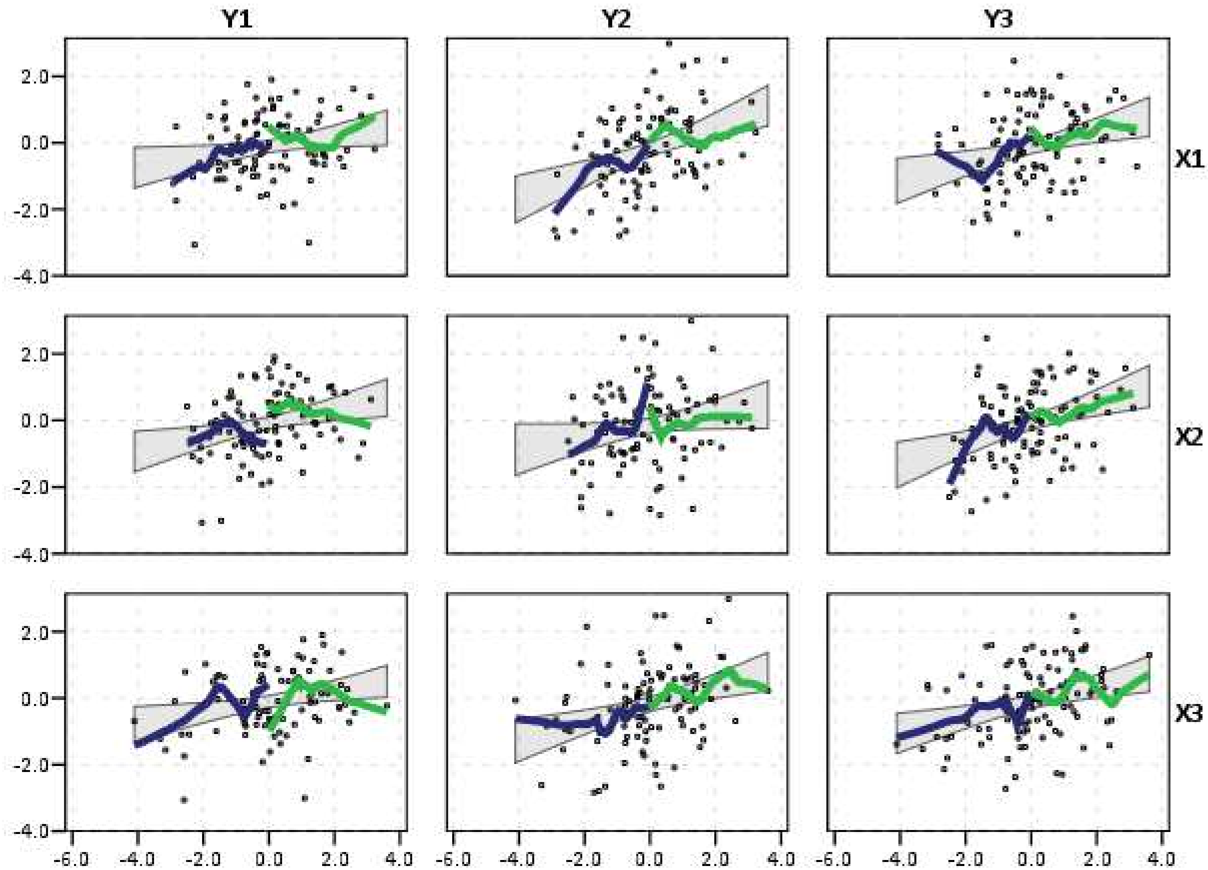
		Frequency	Percent	Valid Percent	Cumulative Percent
Valid	Disagree	10	8.1	8.1	8.1
	Somewhat agree	49	39.5	39.5	47.6
	Neither agree nor disagree	12	9.7	9.7	57.3
	Agree	46	37.1	37.1	94.4
	Strongly Agree	7	5.6	5.6	100.0
	Total	124	100.0	100.0	



Lines are Loess Smoothers by Median Split. Grey area in background is 95% confidence interval for linear regression of X on Y by panel.

Results

The results of regression analysis with the p< 0.05, shows that there is a significant relationship between sodium serum and mode of delivery, Sodium serum, Hemoglobin fluctuations, Gestational age, and Respiratory issues. A survey has been conducted in the hospitals having nurseries to treat the preterm neonates, the neonatologists took part in the survey, it is found that a high rate of "agree" and "strongly agree" was reported to find the relationship between hypernatremia & Intra-ventricular hemorrhage in very & extremely preterm neonates. The same was plotted and found significant values of coefficient and residuals. The residuals are randomly plotted as it the condition of a linear regression.

Conclusion and Discussion

Hypernatremia is found quite often among preterm neonates. However, the major cause of hypernatremia in preterm neonates is dehydration rather than excessive intake of sodium.[34–36]. The study has been designed to evaluate extremely preterm neonates with GA ≤ 26 weeks and BBW ≤ 1000 g, admitted to different hospitals during the 30 years. The data has been collected every month from 1990-2019. It is found that hypernatremia is a major risk factor for IVH in extremely preterm neonates.

The majority of hypernatremia in preterm neonates is caused by dehydration rather than excess sodium intake.9–12 In preterm neonates with a GA <26 weeks, insensible water loss could be as high as 200mlkg1 per day; besides, early diuresis and negative water balance can lead to isotonic dehydration of the extracellular fluid compartment and subsequent postnatal weight loss during the first few days of life. An initial loss of 10 to 15% of body weight is common among very low birth weight preterm neonates, but serum sodium concentrations remain within the normal range. Using a case-matched design, the GA and BBW were controlled in the current study. The net BW loss was less than 10% of the BBW in both groups, and there was no difference in the amount of fluid and scale of BW change during the first 3 postnatal days. Taken together, the phenomenon of hypernatremia in the severe IVH group could not be explained solely by dehydration. Hypernatremia is related to a high mortality rate in patients with subarachnoid hemorrhage. Intracerebral hemorrhage results in the destruction of the hypothalamic nuclei, a reduction in the secretion of antidiuretic hormones, and hypernatremia; hence, hypernatremia in preterm neonates with severe IVH may be the result of severe brain damage. Contrary to this, hypernatremia had been shown a cause of brain shrinkage.[37–39]It is resultant of vascular rupture along with cerebral bleeding and IVH. In response to brain shrinkage induced by hypernatremia, the human brain initiates an adaptive response to form radiogenic osmoles that increase intracellular sodium that has been concentrated and restored lost water. However, this phenomenon raised the susceptibility of the brain towards hemorrhage and cellular edema. It is also explored and has been reported that the change in the level of serum sodium within 13meql has a significant association with the development of the outcomes of impaired function after adjusting for GA besides, hospitalization characteristics of neonatal and perinatal. This study has explored the change in the level of serum sodium levels in 13meql associated with severe IVH, consistent with the results of previous researches. [24–26] Similar to the previous research, our results indicate that males' preterm neonates have an increased risk of developing severe IVH. There found a gender orientation regarding hypernatremia & Intra-ventricular hemorrhage. The male preterm neonates have a higher cerebral flow of blood with a high rate of blood pressure incidents that change the results of norepinephrine, deregulation of and serotonin levels associated with sodium serum, a shred of evidence was found in an animal study (examination). The contributing factors to reperfusion injuries and hypo perfusion in premature babies have been discussed. It is also augmented that by rupturing involution germinal matrix vessels would lead to IVH. The frequent fluctuations in hemoglobin level are also found to have an association with severe IVH explored in our study. A lower level of hematocrit during the first 24h of an infant's life is highly correlated with increased incidents of IVH. Moreover, anemia has an increased flow of cerebral blood that leads to hemorrhage. Furthermore, some of the research found that IVH is associated with vaginal delivery; however, it is controversial to say as the evidences found in favor and contrast. Moreover, it is found that vaginal delivery is a risk factor for severe IVH. We have found that there is a significant relationship between hypernatremia & Intra-ventricular hemorrhage in very &

extremely preterm neonates. The mode of delivery, Sodium serum, Hemoglobin fluctuations, Gestational age, and Respiratory issues are the significant

To address the objectives of this study, it is found that hypernatremia is a major risk factor for IVH in extremely preterm neonates. It is explored that the incidence of hypernatremia in extremely preterm neonates' preterm neonates along with other contributing factors. It is recommended for future research to find other contributing factors to examine this research in further detail.[3–5, 40–44]

Implications

This study contributes to literature by providing a new combination of variables affecting hypernatremia & Intra-ventricular hemorrhage in very & extremely preterm neonates. This study consists of handsome data set so the results are considered as generalizable.

Declarations

Ethics approval and consent to participate

"Not applicable"

Consent for publication

"Not applicable"

Availability of data and materials

Not applicable

Competing interests

"The authors declare that they have no competing interests".

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There is no funding involved in this research.

Authors' contributions

Main author is MHMZ. HJ and AQN helped in collection of data. Also, VN, MY and MHM, and AM are co-authors and also contributed in data collection. JL helped in the research proposal and also provided guidance throughout the research.

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Figures

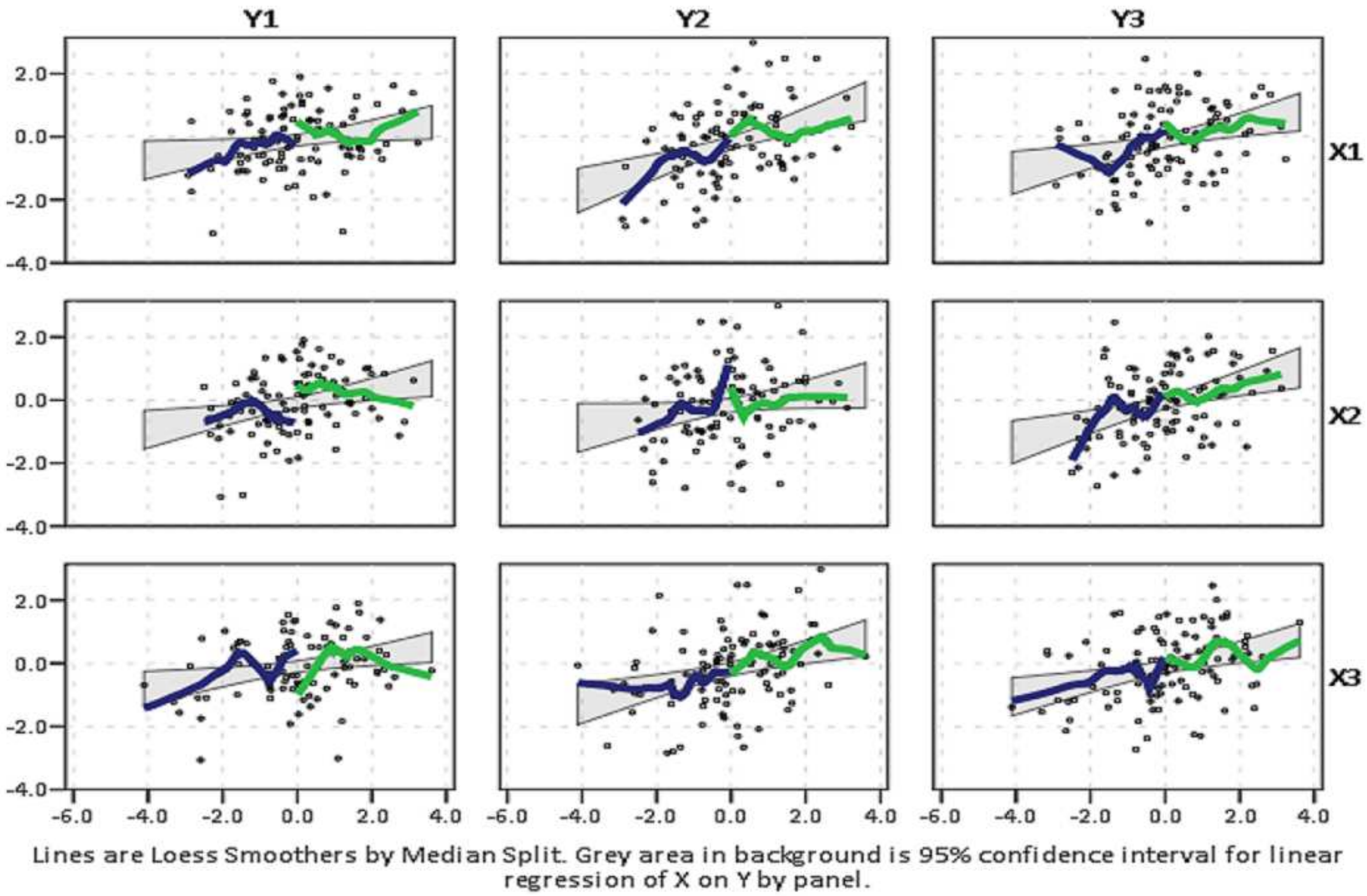

Figure 1

Lines are Loess Smoothers by Median Split. Grey area in background is 95% confidence interval for linear regression of X on Y by panel.

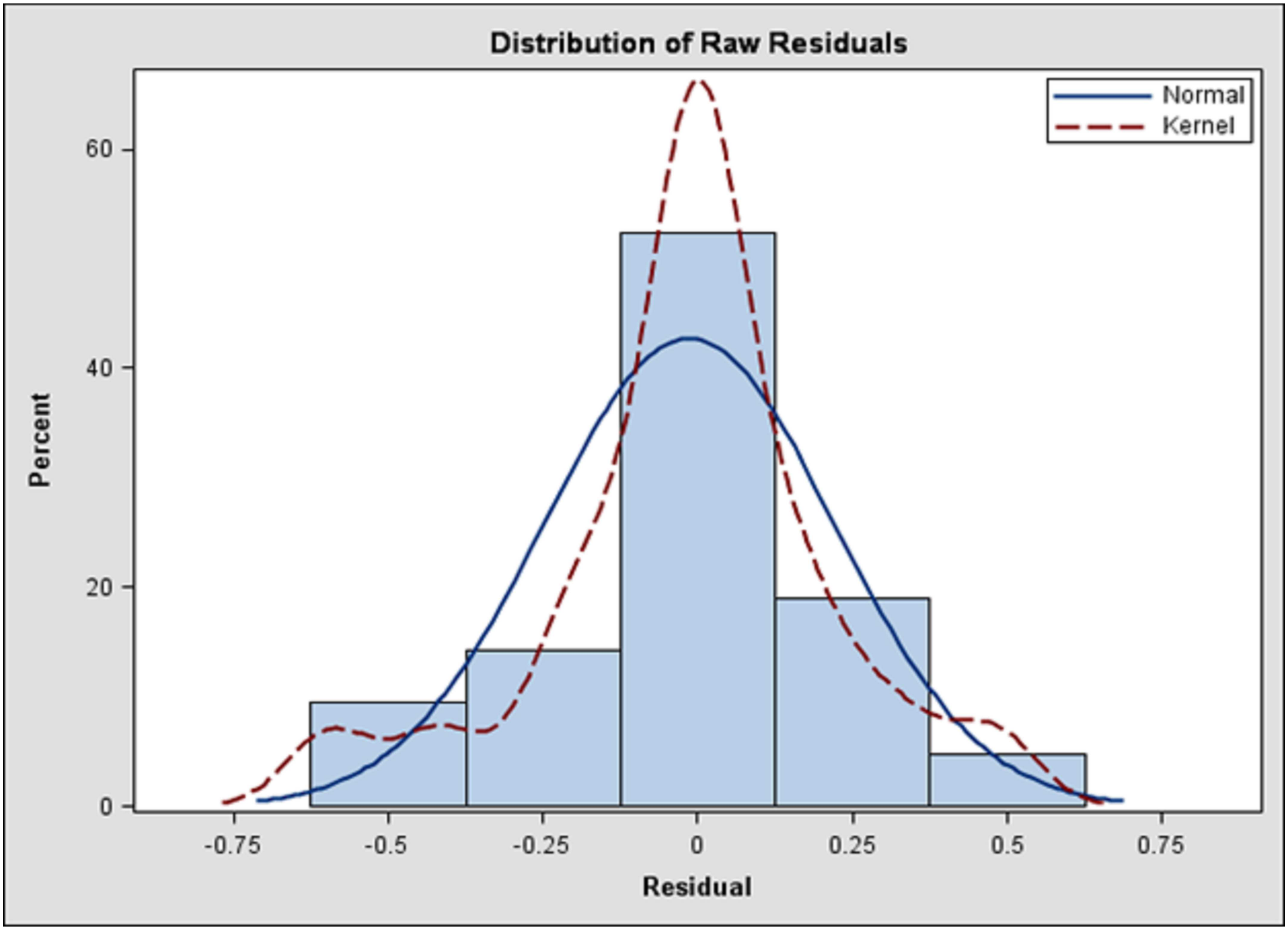

Figure 2

Distribution of Raw Residuals