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Relationship between hypernatremia and intraventricular hemorrhage in very and extremely preterm neonates: A literature review

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Abstract

The purpose of this study is to distinguish the important risk factors that contribute to intraventricular hemorrhage (IVH) and hypernatremia in early postnatal life of the preterm neonates having extremely low birth weight. The study seeks to find a relationship between the two pathologies in neonates born before term and its relevance in this era and age. Intracerebral hemorrhage ends in the damage of the hypothalamic nuclei, a decrease in the secretion of antidiuretic hormones, and hypernatremia; hence, hypernatremia in preterm neonates with severe IVH may be the conclusion of severe brain damage. Contrary to this, hypernatremia had been shown to cause brain shrinkage. A chronological study would be used to compare both, and the goal is thus, to analyze and form an opinion about the topic on the basis of research in a chronological order.

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Introduction

Intraventricular hemorrhage (IVH) has been identified as a frequent consequence in preterm neonates having extremely low birth weight and with the gestational age (GA) matching appropriately with their birth body weight (BBW). A number of studies suggest that hypernatremia contributes to this mix, especially. The scope of this review is to delve thoroughly through a set of researches from the last ten years to discern the relationship between both, intraventricular hemorrhage and hypernatremia in premature neonates. Intraventricular hemorrhage (IVH) is quite often observed as a source of neonatal morbidity among extraordinarily premature preterm neonates. It leads to adverse sequelae on the development of neurons. Some of the factors that associated to IVH were male gender, breakup of brain membranes at a premature stage, delivery method, postnatal resuscitation, the onset of sepsis at a very early stage, hypoxemia, syndrome of respiratory distress, pneumothorax, hypercarbia, and hypocarbia as shown in **Fig. 1** [1, 2]. Furthermore, it was reported that IVHs were observed to be very more common among preterm neonates with hypernatremia. The IVH pathogenesis is multifactorial; it includes, broadly, the germinal fragility matrix vasculature, blood flow fluctuation in cerebral, and platelet and coagulation disturbances[3].

However, the association between intracranial hemorrhage and hypernatremic dehydration has been well-defined among pediatric patients and newborn preterm neonates. However, initially, it was uncertain whether the early fluid alteration or level of serum sodium would affect the severe IVH occurrence in preterm neonates. Therefore, the review of a few studies revealed a possible association between IVH and hypernatremia. The purpose of this study was 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 neonates with low birth weight preterm neonates [4-6]. Sodium is a vital source of muscle function and nerves. The body keeps balanced sodium with a variety of mechanisms. The Sodium level in preterm neonates is determined by the food and drink of the mother. However, high levels of sodium are able to source an increase in the blood pressure resulting in intraventricular hemorrhage of neonates [7, 8]. Also, according to [9, 10] the sugar level (very low or very high) leads to hypernatremia & intraventricular hemorrhage in preterm neonates.

In this literature review, most of the material was available easily on PubMed/MedLine and EMBase in the age group pertaining to the review within the last ten years, with additional studies that focused on the contributing risk factors as well.

Review of the literature

IVH vs. Hypernatremia

Intraventricular hemorrhage (IVH), which was previously undetectable has now with the help of CT (Computed Tomography) scans been able to provide brain imaging in not only neonates but also extremely preterm neonates. As a result, intraventricular hemorrhage along with its extensions can be viewed promptly on a CT scan (**Fig. 2**). It was further revealed that predisposing factors to intraventricular hemorrhage include respiratory distress syndrome, acidosis, hypercapnia, etc. [11, 12]. Therefore, during the last decade, the incidence has declined but still, IVH is considered a highly significant risk factor for morbidity and mortality among extraordinarily premature preterm neonates. The literature revealed that in approximately 90% of the cases, IVH has occurred during the first three days of postnatal life. Intraventricular hemorrhage (IVH) is considered as the supreme significant element that causes mortality amongst those who had developmental impairment during long run in preterm neonates.

Another literature revealed that in a retrospective analysis, neonates having completed less than a twenty-seven-week gestation period developed plasma sodium greater than 145mmol/L (hypernatremia) within the first five days of life. Birthweight, gender and increased insensible water loss seemed to be of no significance and yet neonates that had developed CLD, PDA and IVH had died [13-15].

In fact, the incidence of developmental disability in extremely preterm babies with very low birth rate has been identified to cause intraventricular hemorrhage and even germinal matrix intraventricular hemorrhage as a result of infarcts caused by turbulent blood flow of the brain since this region contains vessels that lacks some components of a completely formed blood brain barrier (BBB), like BM deposition, tight junctions, and glial endfoot investiture[16, 17]. As a result, the ventricles distend, and the rate of blood flow decreases which causes stasis and activates cyclooxygenase 2 (COX-2)

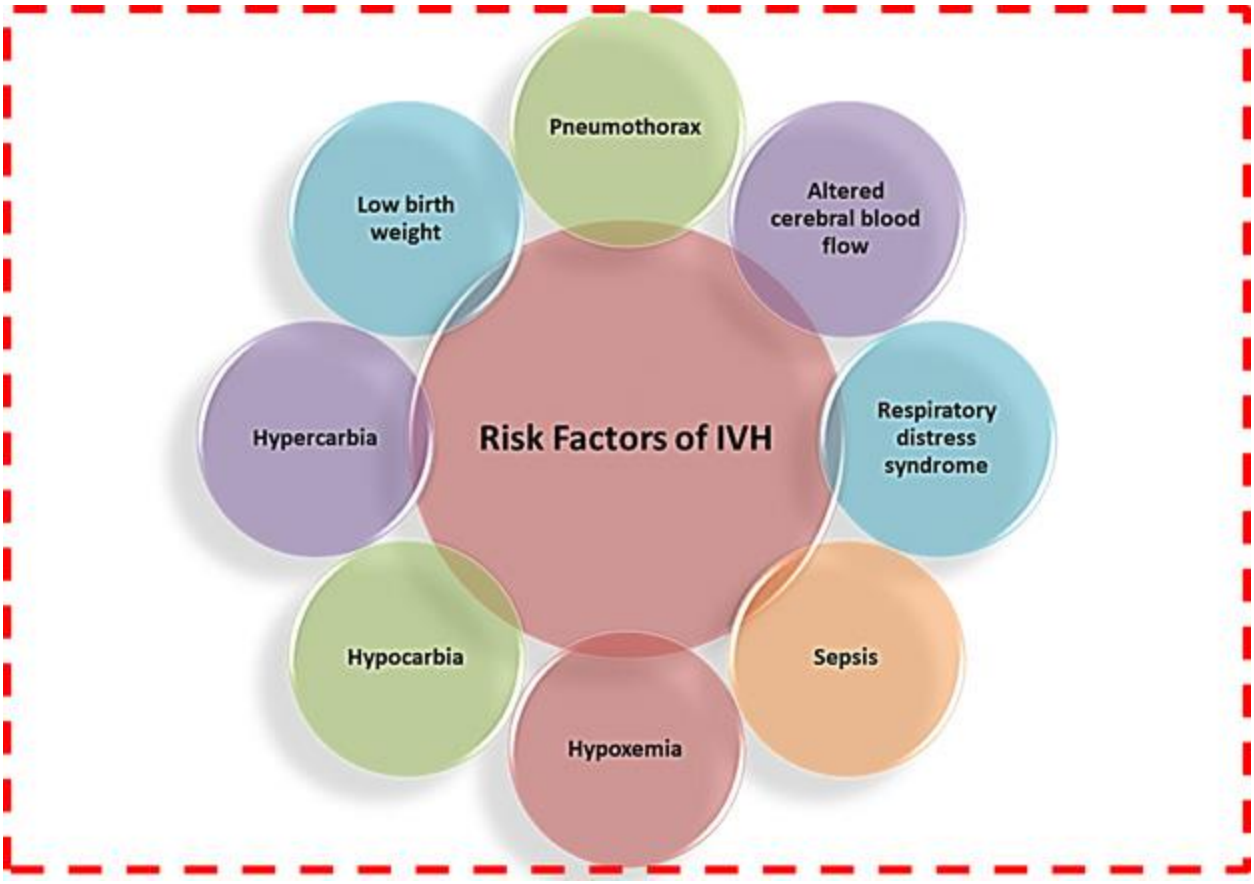

Fig. 1. Risk factors of IVH. Important risk factors that may causes intraventricular hemorrhage (IVH) and hypernatremia in early postnatal life of the preterm neonates with extremely low birth weight.

system and prostaglandins stimulated by hypoxia and hypotension. This results in the production of VEGF (vascular endothelial growth factor), a factor that serves as a potent stimulator for the formation of new blood vessels. This sets into motion the disruption of the blood brain barrier within the periventricular white matter. Thus, the microglia release the hazardous reactive oxygen species that contribute to more damage in the preterm brain than they do in the adult brain by causing damage to the endothelium, altering the hemostasis and increasing anaerobic metabolism. In addition to this, ROS stimulates the activation of the cyclooxygenase 2 system. The multifactorial effect of all of these in turn leads to infarctions in the brain[18]. Genetics might also play a vital role in the pathogenesis of intraventricular hemorrhage but more important that that is to take into account the relation between gestational age and IVH. About 90% cases of hemorrhage are discovered by the end of the first week of the postnatal life of a neonate regardless of their gestational age. This goes to show that gestational age (GA) does not pose as a danger influence for intraventricular hemorrhage in preterm neonates. The literature revealed that prevention for IVH must focus on its environmental and genetic causes [19].

The basic definition of hypernatremia would be when the level of serum sodium is above 145mmol/L. Hypernatremia is not a rare occurrence in the general population and so is of little, if at all, risk if given prompt treatment. If proper management is not provided, hypernatremia can be the cause of mortality. Vasopressin and thirst maintain a normal osmolality in the body in a range of 280 to 295 mOsm/kg. Dysfunction in the aforementioned factors can lead to hypernatremia. In neonates, however, this phenomenon is still being researched upon. The main cause in preterm neonates that leads to abnormal sodium levels in the blood is more often due to excess or loss of fluid intake, rather than excess intake of sodium. Insensible water loss (IWL) is very common in preterm infants in contrast to infants that have completed term because of a greater ratio of surface area to body weight and the presence of non-keratinized skin in extremely preterm neonates which allows great loss of water from the body, since this

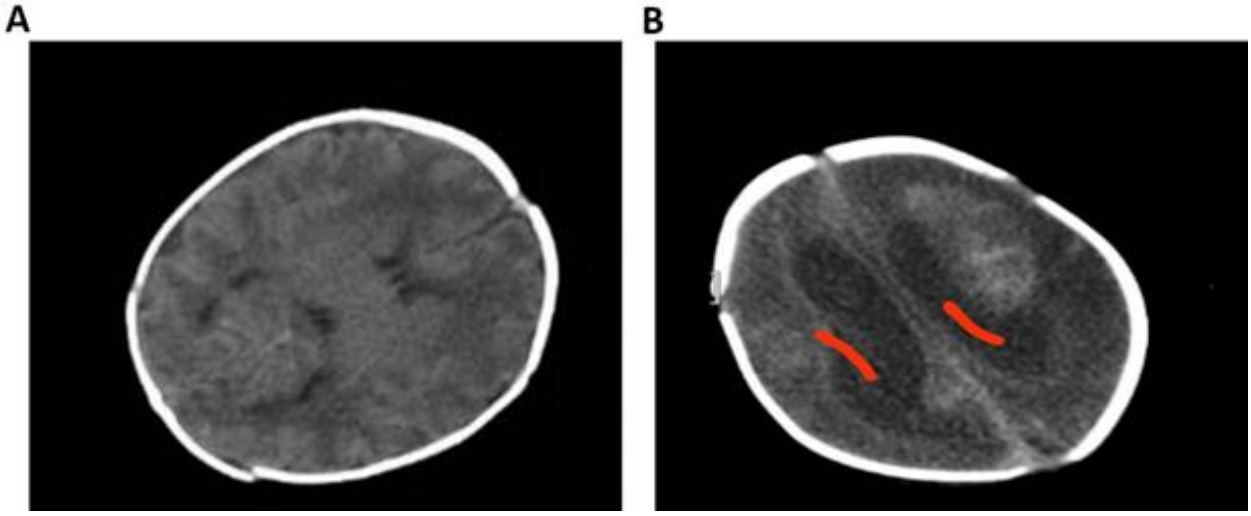

Fig. 2. CT scan images. CT scan results of normal (A) and intraventricular hemorrhage patient (B).

process speeds up in the last trimester of antenatal life. Average water loss in term infants is 20-40 mL/kg/day but in infants with gestation age of less than twenty-six weeks, this loss can be over or equal to 200 mL/kg/day. Another factor that contributes towards hypernatremia is nephrogenesis in the neonate which is achieved completely in the neonate at the 34-36 weeks of gestation[20]. In preterm neonates, this means that the kidneys are not fully functional and correlate to a glomerular filtration rate that is pretty low and nephrons that are still immature. This further leads to decrease in the excretion of extra fluid and electrolyte from the body and decreased production of urea due to high anabolic state in the body. Complications of hypernatremia in a preterm infant include intraventricular hemorrhage, thrombosis and edema of the brain, CVS collapse and severe hyperbilirubinemia[21]. The literature confirmed that out of all the predisposing factors that correlated to hypernatremia, low birth weight contributed the most and babies that were more immature were more likely to develop hypernatremia. The extracellular compartment causes the postnatal weight loss due to isotonic dehydration as a result of water balance that is negative and diuresis. Changes in the concentration of sodium can cause shifts of water inside and outside the ECF which may prove fatal in extremely preterm neonates[22]. Hypernatremia of the neonate is a serious condition that manifests as dehydration due to abnormally increased levels of sodium in the breast milk and is usually secondary to lactation that is insufficient. Neonatal hypernatremia is a dangerous condition because of the consequences like IVH, cerebral edema, hydrocephalus and gangrene. Neonates lose some of their birth weight through the first week of their life, normally and regain it back by the tenth day of their postnatal life. However, if there is a constant decrease in birth weight, even after the first two weeks of postnatal life, it should ring alarm bells because this is the first sign of neonatal hypernatremia. There are a few causes that lead to increased levels of blood glucose galactopoiesis because of a sick neonate and less frequency of breast stimulation and drainage and the other factor was low birth weight of gestational age of the neonate [23-25].

Sodium & fluid intake and its effect and association with intraventricular hemorrhage

Most of the literature reviewed suggested that hyponatremic dehydration and intraventricular hemorrhage (IVH) go hand in hand, especially their associations in infants that are born preterm and with low birth weight. As previously stated, IVH is one of the most rising causes of mortality and developmental abnormalities in preterm neonates. The more severe the IVH, the greater the developmental abnormality. That is to say, Grade III and Grade IV IVH are prone to more neurological sequelae than Grade I and Grade II IVH, according to the Papile classification. Severity of IVH, in turn, depends mostly upon low birth weight[9]. In relation to intake of sodium and balance of fluid, it has been discovered that the risk of severe IVH increases with increased sodium intake within the first for days of postnatal life, especially in neonates with extremely

low birth weight. Lupton et al. shown that an excessive serum sodium concentration throughout the initial four days of life, when defined by serum sodium > 145 mM/L or > 152 mM/L, was not associated with an increased danger of IVH in VLBW infants. A study by Perrott et al established the relationship of high blood sodium levels with major disabilities of the brain development in infants with a gestational age of less than thirty weeks although no strong association with IVH was proved [26, 27]. The hypernatremic dehydration caused hemorrhage in a preterm neonate shows diffuse lines of lesions, especially in the junction between the gray and white matter of the brain and in multiple parenchymal sites which may further lead to encephalomalacia. Hence, the literature reveals that sodium imbalance may have several outcomes on the neonate, the most important of which is IVH, while others also include, PDA, RDS, sensory hearing loss or impairment and developmental disabilities, mostly of the motor origin [26]. 'Preterm neonates are at the greatest risk of hypernatremia [17, 28].and later of hyponatraemia [29, 30]. Hypernatraemia has been variably defined as a serum sodium > 145 mmol/L (Balasubramanian 2012) or ≥ 150 mmol/L [31, 32]; and hyponatraemia as a serum sodium < 135 mmol/L [33] or < 130 mml/L [34-36].' Water and sodium balance is showcased in the serum sodium level and this changes a lot after postnatal life, especially due to ECF because it contracts after birth as a result of negative water and sodium balance and proceeds to cause loss of water. The rest of the water loss is because of transepidermal loss of water especially in extremely low birth weight neonates [30]. Higher excretion of sodium by the kidney increases the tendency for high levels of serum sodium in the body even though there is a low glomerular filtration rate initially[37]. Thus, in the first few weeks of postnatal life, water intake of neonate is modified to balance the changes in sodium serum or other causes of hydration. Preterm infants have high fractional excretion of sodium (FENa) secondary to impaired tubular sodium reabsorption [38-41]. Despite a relatively low GFR, it is thought the increase in GFR over time frequently exceeds the limited tubular sodium reabsorption capacity in very preterm infants [42, 43].Reported risk factors for hyponatremia include increasing prematurity [44], birth weight of less than 1000 grams, feedings of fortified human milk and occurrence of an intraventricular hemorrhage [45]. Intake of sodium in preterm infants is from a combination of both, parenteral and enteral sources. The European Society for Paediatric Gastroenterology, Hepatology and Nutrition (ESPGHAN) however, suggest the usage of parenteral sodium intake in neonates that are preterm in order for them to adapt more easily to it[46].

In the initial phase of transition, it is suggested for the net negative sodium balance to reach a range of 2 to 5 mmol/kg and during the next phase, that is, the intermediate phase, to allow the body to counter the losses of electrolytes and replace them. In the third and final phase, that is the growth phase 3-5mmol/kg/day must be provided for two things; to replete the body for losses and to build new tissue to increase growth rate. ESPGHAN recommendations for enteral intakes are 3 to 5 mmol/kg/day [47]. Thus, for easier understanding, early higher sodium supplementation is defined intake of parenteral or enteral dosage of ≥ 2 mmol/kg/day; and later higher sodium supplementation is defined as intake of parenteral or enteral dosage of ≥ 5 mmol/kg/day, and lower sodium supplementation as < 3 mmol/kg/day. Restriction of sodium especially in fluids that are parenteral reduce the chances and severity of the hyponatremia that may follow and sodium requirements may easily be fulfilled by intake of water but only in the early cases of hyponatremia because later cases of hyponatremia are more often than not benign conditions. Sodium is vital for electrolyte and fluid therapy in extremely preterm neonates. Postnatal growth failure is of common incidence to them as well so it is important to reduce their morbidity and mortality levels by optimising their sodium intake[48].

So, in a nutshell, it is important to provide early management and treatment to preterm neonates having hypernatremic dehydration because its consequences are extremely severe as it cause shrinkage of the neonatal brain which is followed by huge influx of solutes into the brain cells to allow restoration of normal brain volume as an adaptive response. This rapid response can for the correction of hypernatremia can cause cerebral edema that can lead to the rupture of the vessels in the cerebral space and cause subarachnoid hemorrhage, intraventricular hemorrhage or permanent brain death [49]. There has been a rising body of literature reporting a relationship between hypernatremia and IVH in preterm neonates. Apart from this, risk of severe neurological complications can increase in extremely preterm neonates as a result of rapid correction of serum sodium. That is why a serum sodium adjustment rate of less than 0.5 mmol/L/h or 10 mmol/L/d delivers better results and it has been highlighted that the highest rate of decrease of the

serum sodium level in term neonates with hypernatremic dehydration should not exceed 0.6 mmol/L/h or 15 mmol/L/d17. In conclusion, hypernatremia is individually related with any IVH, or severe IVH or death throughout the first 10 days of life. It therefore looks suitable to follow the same guidelines that have been used in term neonates and elder infants to treat hypernatremia in ELBW preterm infants as well [50].

Pathogenesis

In the first few days of postnatal life, intraventricular hemorrhage accounts for at least 1-2 out of a 1000 liveborn infants. This incidence further increases with decrease in the gestational age and low birth weight of the infant and at least 25% of these infants are said to have IVH at autopsy. These hemorrhages are usually due to bleeding of the veins that are present beneath the ependyma close to the lateral ventricle. There is a great incidence of hypoxia with IVH for obvious reasons, but the basic pathogenesis of intraventricular hemorrhage is as follows. Asphyxiation/trauma at birth, distortion of the terminal veins, thrombosis of the germinal matrix plate and hypoxia can all be causes of the bleeding in relation to IVH [51, 52]. The very significant factor in the pathogenesis of both huge pulmonary hemorrhage (or hemorrhagic pulmonary edema) and IVH is possibly elevated venous and capillary pressure following myocardial failure due to asphyxia. Because we have seen, in severely asphyxiated infants (unpublished data), the occurrence of plasma filtrates in the pleural, pericardial, and peritoneal spaces as well as in the urine, which occasionally also contains red blood cells, we recommend that a variety of disorders in the newborn stage may outcome from elevated intravascular pressures [53].

Preterm infants when surviving through their first postnatal day undergo a bout of hypotension and low cardiac output which in turn causes them problems in maintaining adequate perfusion to their brain. Moreover, since the pressure range of autoregulation decreases with decrease in gestational age, poor cerebral perfusion can obviously take place. Apart from this, the anatomical factors like incomplete growth of the arterial system into the germinal matrix vasculature can provide the details behind severe occurrence of intraventricular hemorrhage as well and all of this happens in the third trimester of prenatal life. This region of fragile vasculature and the lack of cerebrovascular resistance are the primary parameters for IVH. After anatomical, we discuss the histological risk factors for IVH which include chorioamnionitis, an infiltration of the maternal neutrophils in the chorion and amnion, and umbilical vasculitis. Chorioamnionitis will be discussed later in this review in more detail. The study further revealed that persistent PDA, thrombocytopenia, necrotizing enterocolitis and hypernatremia in the preterm neonates were also important risk factors. Antenatal steroids help in maturation of the choroid plexus which is why they are proven to help decrease the incidence of IVH [54]. Delivery of the neonate through Cesarean section, indomethacin management, synthetic hemostatic agents that improves capillary resistance via platelet adhesion, birth weight greater than 1000g and gestational age within 27-28 weeks also predicts the decreased incidence of intraventricular hemorrhage in neonates. Prophylactic synthetic surfactant induced to the neonate for management of acute RDS, pneumothorax and pulmonary edema, all pathologies that showcase as risk factors for IVH, have however shown no effect on its incidence. Interventions given to preterm neonates to save their lives like transfusions of RBCs have seen to cause greater risk in developing IVH.

Extremely preterm neonates are more susceptible to IVH and hypernatremia due to evaporation of H_2O and its loss per kg of body weight and renal immaturity. Fillipi *et al.,* also informed 2 cases of hypernatremia in 2 extremely low birth weight infants. One infant developed hypernatremia up to 167 mmol/l and lived exclusive of any problems. The other infant had plasma sodium levels of 166 mmol/l. She developed severe bilateral intraventricular hemorrhage and expired. In summary, earlier literature shows us conflicting results in neurological result after hypernatremia in preterm infants. Lupton et al. reported no rise in intraventricular hemorrhage related to extreme sodium levels between 152 and 160 mmol/l, whereas Perrott et al. found that hypernatremia is associated with the development of main disability in infants among 22 and 30 weeks of gestation. This concludes that even severe hypernatremia does not inevitably lead to CNS dysfunction and seizures in extremely low birth weight infants. The etiology of hypernatremia inevitably marks clinical result and influences prognostic factors of further neurological development. Thus, hypernatremia in extremely low birth weight infants affected by infusion error has a superior prognosis than hypernatremia affected by dehydration [55, 56].

Imaging, detection & prognosis

A 2010 literature revealed that the association of intraventricular hemorrhage in preterm neonates was in fact, multifactorial, taking into consideration the sodium intake and hypernatremia as well. Around 722 preterm infants were charted from 20022 to 2006 and reviewed daily for serum sodium concentrations. Grade II and Grade IV IVH was seen to be found in preterm neonates with increased sodium intake and increased serum sodium concentration in the first three days of postnatal life. This discussed the possibility of high sodium intake to represent as a modifiable risk factor in extremely preterm neonates for intraventricular hemorrhage [57]. A case control study to study preterm infants with a GA $\leq$ 26 weeks and a BBW $\leq$ 1000 g. It was revealed that along with gestational age and birth body weight, PV delivery, male gender, high levels of serum sodium and fluctuations in pH, partial pressure of carbon dioxide, hemoglobin count and platelet counts factored enormously to the risk of intraventricular hemorrhage. Head ultrasound (HUS) is used to evaluate IVH as well as brain MRI and susceptibility weighted neuroimaging (SWI) because where HUS has higher sensitivity and specificity than the latter in detecting grade III GMH, susceptibility weighted imaging can better detect a grade II GMH. Germinal matrix hemorrhage is the greatest usual form of intraventricular hemorrhage in premature neonates. The stages of it were put forward by Papile in 1978, based on the VLBW infants: Grade I hemorrhage is limited to the subependymal tissues, Grade II IVH shows hemorrhage with no ventricular dilation, Grade III shows hemorrhage with ventricular dilation, and Grade IV IVH includes infarct of the intramedullary vein due to impaired drainage of the veins or because of periventricular hemorrhagic infarction (PVHI). Since Grade I GMH-IVH is a mild case with a benign course, it requires no MRI or HUS in the premature neonates as this renders it impossible to determine both the tests specificity and sensitivity[58]. However, for Grade II GMH, HUS provides terrible sensitivity which leaves us with the SWI technique that has proven that it can help detect even the smallest hemorrhages are better visualized. In the case of Grade II GMH, all modalities provided great sensitivity and specificity, primarily because of the dilation of the ventricle, this includes the HUS, MRI and SWI. Grade IV hemorrhage can be demonstrated on head ultrasound and magnetic resonance imaging as a fan shaped lesion on the area surrounding the ventricle. But as with Grade II IVH, HUS is yet again only sensitive for extensive PVHI but for small, focal PVHI, the technique of choice will be SWI. Thus, in short, to detect the microhemorrhages in preterm neonates, use of SWI must be established and must be presumed as an excellent tool for detecting hemorrhages in premature neonates that are not visible on the standard MRI, since they not only help detect IVH but also enable us to gather data on other neurological sequelae that are common in infants, including neoplasms, infarcts and thromboses [59, 60].

Predisposing and risk factors of IVH vs. hypernatremia

Thus far it has been implied again and again that germinal matrix intraventricular hemorrhage is the most common neurological lesion discovered in neonates having low birth weight or gestational age. A subset of preterm neonates, however, that fall in this same category are also at the risk of developing PHVD or post hemorrhagic ventricular dilation which may either be due to post hemorrhagic hydrocephalus that progresses due to raised intracranial pressure or due to hydrocephalus in the presentation of encephalomalacia. It is of vital importance to know about this as these pathologies can be challenging to manage in a preterm infant. Another neurological entity separates from IVH but detectable on MRI and HUS is cystic periventricular leukomalacia (cPVL). IVH can more often than not appear in combination with cPVL. The main hypothesis behind this is that preterm infants when surviving through their first postnatal day undergo a bout of hypotension and low cardiac output which in turn causes them problems in maintaining adequate perfusion to their brain. Moreover, since the pressure range of autoregulation decreases with decrease in gestational age, poor cerebral perfusion can obviously take place. Apart from this, the anatomical factors like incomplete growth of the arterial system into the germinal matrix vasculature can provide the details behind severe occurrence of intraventricular hemorrhage as well and all of this happens in the third trimester of prenatal life. This region of fragile vasculature and the lack of cerebrovascular resistance are the primary parameters for IVH. After anatomical, we discuss the histological risk factors for IVH which include chorioamnionitis, an infiltration of the maternal neutrophils in the chorion and amnion, and umbilical vasculitis.

Chorioamnionitis will be discussed later in this review in more detail. The study further revealed that persistent PDA, thrombocytopenia, necrotizing enterocolitis and hypernatremia in the preterm neonates were also important risk factors. Antenatal steroids help in maturation of the choroid plexus which is why they are proven to help decrease the incidence of IVH. Delivery of the neonate through Cesarean section, indomethacin management, synthetic hemostatic agents that improves capillary resistance via platelet adhesion, birth weight greater than 1000g and gestational age within 27-28 weeks also predicts the decreased incidence of intraventricular hemorrhage in neonates. Prophylactic synthetic surfactant induced to the neonate for management of acute RDS, pneumothorax and pulmonary edema, all pathologies that showcase as risk factors for IVH, have however shown no effect on its incidence. Interventions given to preterm neonates to save their lives like transfusions of RBCs have seen to cause greater risk in developing IVH [61].

Term neonates have also shown incidence of intraventricular hemorrhage but with different etiologies, presentations and results. IVH in neonates presents as dilation or blood occluding the ventricles of the brain, namely the third, fourth and lateral ventricles. Although, IVH is more common in preterm neonates, it is not completely invisible in neonates of term too. These groups of neonates present to the NICU with seizures followed by fever and poor feeding patterns. Less common symptoms involve Damage of pupillary reflex, loss of movements of the extraocular muscles, respiratory difficulties, vomiting, coma, palsy of the gaze, shrill cry, decreased tone of the lower extremity, opisthotonic posturing of the body, weakness of the central face, hypothermia, hyperglycemia, head lag and decreased overall reflexes. Major sites of bleed were the choroid plexus, the germinal matrix and the parenchyma. The same sites as in preterm neonates. The only difference up till now is the presentation of symptoms and one site is the choroid plexus, where there is no proof of IVH occurence in extremely preterm neonates. The most probable reason for this has to be the degree of maturity of the cerebral tissues in the term neonates in contrast to the preterm neonates[62]. Furthermore, the risk factors in this scenario correlate more to coagulopathies, maternal preeclampsia, infections of the urogenital tract, CA and neonatal problems like asphyxia, trauma, deficiency of Vitamin K rather than respiratory disorders, male gender, fragility of vasculature in the germinal matrix or mode of delivery as are the risk factors for preterm IVH. Consequences of intraventricular hemorrhage in both the groups are, however, not as dissimilar as they should be. Both term and preterm neonates show adverse neurological development and maybe, probably death on the onset of severe IVH. Severity of symptoms of IVH have always depended largely on the degree and size of hemorrhage. And as far as complications are concerned, PHH, periventricular leukomalacia and atrophy of cerebral tissue are still more common in this case. Mortality rate of Grade IV germinal matrix intraventricular hemorrhage is most at least in Grade I GM-IVH, however the commoner grades of IVH to occur in neonates that have normal gestational age are Grade III and IV. Hypernatremia was seen related to IVH in both cases of term and preterm neonates[63].

Chorioamnionitis in relation to IVH and hypernatremia

Chorioamnionitis (CA) is also a common risk factor in the disease of prematurity of 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 ideal 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 [64]. 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[24,25,27]. Contrary to this, the funisitis

presence has not shown 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 [65]. 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 visible to CA. Nevertheless, multiple regression analyses do not demonstrate proper association between the IVH and hypoxemia in lower GA and BW of the preterm infant. 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 huge 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.

Another research suggested that asphyxiated neonates who were treated for hypothermia passed away also because of intraventricular hypothermia [66].

Many of previous research have proposed several IVH perinatal risk factors also including the following: gestational age (GA) low birth weight gender, lack of antenatal steroids, intrauterine infection, manner of delivery, hyper apnea, hypoxemia, pulmonary hemorrhage, respiratory distress syndrome (RDS), pneumothorax, bicarbonate infusion, and metabolic acidosis [8,35,39].

Water and sodium balance are showcased in the serum sodium level and this changes a lot after postnatal life, especially due to ECF because it contracts after birth as a result of negative water and sodium balance and proceeds to cause loss of water. The rest of the water loss is because of trans epidermal loss of water especially in extremely low birth weight neonates. Higher excretion of sodium by the kidney increases the tendency for high levels of serum sodium in the body even though there is a low glomerular filtration rate initially. Thus, in the first few weeks of postnatal life, water intake of neonate is modified to balance the changes in sodium serum or other causes of hydration. Preterm infants have high fractional excretion of sodium (FENa) secondary to impaired tubular sodium reabsorption. This explains the relation between CA, IVH and hypernatremia.

IVH, hypernatremia and hyperglycemia

Another factor that has been recently associated with IVH and its increasing mortality and morbidity rates has to be hyperglycemia since insulin therapy and normal blood glucose levels provide better prognosis in these cases. In fact, increased levels of blood glucose in extremely low birth weight preterm neonates (< 1000g) correlates to increased risk of Grade III and Grade IV intraventricular hemorrhage. It has been discovered that treating extremely preterm neonates with parenteral doses of insulin in the beginning of postnatal life has not been beneficial because of the rise in mortality rate and induction of hypoglycemic states in doing so [67]. And again, as previously established, gestational age less than 38 weeks, respiratory distress syndrome, pneumothorax, thrombocytopenia, hypotension and sepsis contribute greatly to intraventricular hemorrhage as well. However, supportive management in the form of corticosteroid provided to the mother antenatally and indomethacin therapy (given to treat patent ductus arteriosus) of the neonate have shown to decrease the incidence of severe IVH. This still does not, however, shed light on the severe occurrence of intraventricular hemorrhage with hyperglycemia, as was revealed by the study in eighty six percent of the neonates examined 96 hours after their birth. The definitions of both, hyper and hypoglycemia are debatable in infants because no association has been established between the plasma level of glucose with clinical symptoms or neurological sequelae as of yet. Also, since both of these are never exact and revolve around the parameters of severe to mild, it is important to consider the duration, effect and frequency of the abnormal glucose levels too. Thus, in the study, blood glucose level below 3.3mmol/L was deemed hypoglycemia, whereas that in the range of 2.5-2.7 mmol/L was deemed hyperglycemia or quantified as increased blood glucose level in the neonates. It helped in revealing that abnormally high glucose levels for a longer duration, especially in those neonates associated with a significant risk factor for IVH were more prone to the occurrence of a hemorrhage. This long duration of hyperglycemia promised to be at least a ten-hour period, where even a mild increase in circulating glucose levels resulted in prominent intraventricular hemorrhage. Consequently, it was proved that the greater the clinical severity score of hyperglycemia, the greater

the association of severe intraventricular hemorrhage and the greater the increase in the duration of hyperglycemic period in the neonate, the greater the chances for severe IVH in the neonate [64]. Prevention of postnatal IVH in extremely low birth weight neonates is mainly the adjustment of danger influences like resuscitation, identification, thermoregulation and pharmacological intervention. Hyperglycemia in the hypernatremic extremely low birth weight infants during the first 10 days after birth is an independent danger influence for the progress of IVH. Neither hypernatremia alone nor hyperglycemia cured with insulin infusion alone can independently be related with the growth of intraventricular hemorrhage when we run it through the multivariate analysis [68]. Extremely preterm neonates are especially susceptible to increasing hypernatremia owing to high insensible H2O losses, immaturity of the kidney with inability to compensate for alterations in liquid and electrolyte ingestion and excessive urine output. These infants are also prone to grow hyperglycemia because of an exaggerated stress response with increased glucose making, extreme exogenous glucose administration and insulin insensitivity. Both hypernatremia and hyperglycemia tip to hyperosmolarity and osmotic shifts, and any cause of hyperosmolarity may induce neuronal dehydration and speedy loss of brain capacity. This can outcome in rupture of cerebral blood vessels, cerebral and subarachnoid hemorrhage and long-term irreversible brain injury. Hyperglycemia alone in highest clinical situations does not cause significant adequate osmotic shifts to cause IVH in extremely low birth weight preterm infants. However, the presence of hyperglycemia in mixture with hypernatremia further rises the plasma osmolarity and osmotic shifts, likely compounding the special effects on the brain. Thus, close attention to liquid and electrolyte controlling in extremely low birth weight infants in the first 10 days after birth can reduction their danger of increasing IVH. Such managing will likely be most effective if hyperglycemia is prevented specially in preterm infants who are also hypernatremic [66, 70].

Conclusion

This review contributes to the literature by providing a new combination of variables affecting hypernatremia & intraventricular hemorrhage in very & extremely preterm neonates. It also consists of a review of a handsome amount of relevant data to prove the correlation between the two entities that are intraventricular hemorrhage (IVH) and hypernatremia.

Hypernatremia is found quite often among preterm neonates. However, the majority of the literature points towards the cause of hypernatremia in preterm neonates as dehydration rather than excessive intake of sodium. In preterm neonates with a GA <26 weeks, insensible H2O loss could be as excessive as 200ml to 1kg per day; moreover, initial diuresis and negative H2O balance can lead to isotonic dehydration of the extracellular liquid compartment and subsequent postnatal weight loss during the first few days of life. An early loss of 10 to 15% of body weight is common between very low birth weight preterm neonates, but serum sodium strengths continue within the normal range. Taken together, the experience of hypernatremia in the severe IVH group could not be described solely by dehydration. Hypernatremia is associated to an extreme mortality rate in patients with subarachnoid hemorrhage. Intracerebral hemorrhage outcomes in the damage of the hypothalamic nuclei, a decrease in the secretion of antidiuretic hormones, and hypernatremia; hence, hypernatremia in preterm neonates with severe IVH might be the outcome of severe brain destruction. Contrary to this, hypernatremia had been indicated to source brain shrinkage. It is resulting of vascular rupture along with cerebral hemorrhage and IVH. In reaction to brain shrinkage induced by hypernatremia, the human brain initiates an adaptive reaction to form radiogenic osmoles that rise intracellular sodium that has been concentrated and restores lost water. However, this sensation 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 life. The review has delved into the change in the level of serum sodium levels in 13meql associated with severe IVH, consistent with the results of previous researches. In harmony with the previous researches, our conclusion indicates that male preterm neonates have an increased risk of developing severe IVH. Therefore, finding a gender orientation regarding hypernatremia & intraventricular 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 hypoperfusion in premature babies have been discussed. It is also augmented that the rupturing of involution germinal matrix vessels would lead to IVH. The frequent fluctuations in hemoglobin levels are also found to have an association with severe IVH explored in our review. A lower level of hematocrit during the first 24h of an infant's life is highly correlated with an increased incidence of IVH. Moreover, anemia has 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 evidence is found in both favor and contrast. Moreover, it is discovered that normal delivery is a dangerous influence on severe IVH. We have found through the literature that there is a significant relationship between hypernatremia & intraventricular hemorrhage in very & extremely preterm neonates. The mode of delivery, sodium serum, hemoglobin fluctuations, gestational age, and respiratory issues are significant. To address the objectives of this study, it is found that hypernatremia is the main danger factor for IVH in extremely preterm neonates. It is explored that the incidence of hypernatremia in extremely preterm neonates along with other contributing factors. A few other influences were found to be significantly affecting the preterm neonates, namely resuscitation, vaginal delivery, hemoglobin, male sex, level of high sodium serum, fluctuation of serum sodium, and platelet counts. All of these are also associated with severe IVH and hypernatremia. The review concludes a significant positive relationship between hypernatremia & intraventricular hemorrhage in very & extremely preterm neonates along with other contributing factors.

Conflict of interest

The authors declare no conflict of interest.

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