Open Access Maced J Med Sci **electronic publication ahead of print, published on October 10, 2019 as https://doi.org/10.3889/oamjms.2019.558**

ID Design Press, Skopje, Republic of Macedonia
Open Access Macedonian Journal of Medical Sciences.
https://doi.org/10.3889/oamjms.2019.558
eISSN: 1857-9655
Clinical Science

Prevalence and Risk Factors for Hyponatremia in Preterm Infants

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Citation: Kiem Hao T, Son NH. Prevalence and Risk Factors for Hyponatremia in Preterm Infants. Open Access Maced J Med Sci. https://doi.org/10.3889/oamjms.2019.558

Keywords: Hyponatremia; Preterm newborns; Risk factors

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Received: 16-Apr-2019; **Revised:** 04-Sep-2019; **Accepted:** 05-Sep-2019; **Online first:** 10-Oct-2019

Funding: This research did not receive any financial support

Competing Interests: The authors have declared that no competing interests exist

Abstract

BACKGROUND: Hyponatremia is the result of a negative sodium balance caused by inadequate salt intake or excessive salt loss due to immature renal or intestinal function in preterm infants.

AIM: The aim of our study was to define the incidence of and factors affecting its development in preterm newborns.

METHODS: This was a retrospective cohort analysis of 126 preterm infants born before 36 weeks of gestation between June 2016 and July 2018 at Neonatal Intensive Care Unit of Hue Central Hospital, Vietnam. Hyponatremia was defined as a sodium level ≤ 132 mEq/L or 133-135 mEq/L with oral sodium supplementation. We used the serum sodium level to define hyponatremia.

RESULTS: There were 37 infants who had hyponatremia, accounting for 29.4% of the infants enrolled in the study. A lower gestational age, the presence of respiratory distress syndrome, the use of furosemide, and feeding with breast milk were significant risk factors for hyponatremia in preterm newborns.

CONCLUSION: Hyponatremia occurred at a relatively high frequency. This result exemplifies the importance of serum sodium monitoring and supplementation for the correction of hyponatremia.

Introduction

Sodium, an element essential to growth, is contained in bone, cartilage and connective tissue and is indispensable for the development and operation of the central nervous system. Mild hyponatraemia is common in preterm babies and is not known to cause significant adverse effects [1]. On the contrary, extreme hyponatraemia is rarely seen and increases the risk of neurodisability [2], [3]. Many factors predispose preterm babies to hyponatraemia: impaired reabsorption of sodium at both proximal and distal tubules [4], inadequate salt provision, *e.g.*with donor breast milk [5], immaturity of endocrine mechanisms of water and sodium homeostasis [6]. Hypoxia, medications and respiratory distress can also aggravate hyponatremia associated with kidney tubular damage. However, few studies have addressed the incidence of and risk factors for hyponatremia in preterm newborns is achieved.

In this study, we aimed to define the incidence of and factors affecting its development in preterm newborns.

Material and Methods

Our retrospective cohort was composed of 126 preterm infants born before 37 weeks of gestation and admitted to the Neonatal Intensive Care Unit of Hue Central Hospital, Vietnam between June 2016 and July 2018. The data were collected via a retrospective chart review. The collected data included the infants' perinatal histories, clinical characteristics (including hyponatremia). This study was approved by the Hue Central Hospital institutional review board. Informed consent was waived by the board.

Hyponatremia was defined as a sodium level ≤ 132 mEq/L or between 133 and 135 mEq/L with oral sodium supplementation [7]. According to our nutritional policy, total parenteral nutrition was started from birth and also protein and lipid supplementation was started at day 1. Sodium supplementation was started after diuresis begins according to the capillary or serum sodium level. If there is a hyponatremia, we routinely checked sodium level every 1-3 days to assess whether hyponatremia is relieved. The duration of hyponatremia was defined as the length of

time when the sodium level was ≤ 132 mEq/L. We used the serum sodium level to define hyponatremia.

All the numerical data are expressed as the means±standard deviation. The *t*-test or the Mann-Whitney test was used for continuous variables. The chi-square test or Fisher's exact test was used for the analysis of categorical variables.

To evaluate the risk factors for hyponatremia, we compared the perinatal factors of the hyponatremia and non-hyponatremia groups during the study period. A multiple logistic regression using a stepwise selection was employed, and we included significant variables (those with *P* values below 0.05) in a univariate analysis. The statistical analysis was conducted using SPSS Statistics version 20.

Results

Patient characteristics

A total of 126 infants born at 24 through 36 weeks of gestation were included in this retrospective cohort study. More than one-half of the entire cohort was male (59.5%), and 81% of the births were a singleton.

There were 37 infants who had hyponatremia, accounting for 29.4% of the infants enrolled in the study. The mean gestational age of the hyponatremia group was 29.1 ± 3.2 weeks (minimum-maximum; 23-33 weeks), and their mean birth weight was 973.7 ± 315.9 g (820-2,250 g). The mean onset of hyponatremia was 3.4 ± 1.5 days after birth (1-12 days), and the mean duration of hyponatremia was 3.23 ± 2.18 days (1-6 days). Of the 37 infants with hyponatremia, 13 (35.1%) experienced a hyponatremia duration of at least 4 days. There were no infants with serious neurologic complications associated with hyponatremia.

Risk factors for hyponatremia

The hyponatremia group had a lower gestational age and a lower birth weight than did the non-hyponatremia group (*P* < 0.01). Premature rupture of the membranes occurring more than 18 hr before the delivery, the use of prenatal antibiotics, respiratory distress syndrome, patent ductus arteriosus requiring medical, postnatal culture-proven sepsis, and the use of postnatal antibiotics or furosemide within two weeks after birth occurred significantly more frequently in the hyponatremia group (*P* < 0.05). Feeding with breast milk was more common in the hyponatremia group (*P* < 0.05) (Table 1).

Table 1: Univariate analyses of perinatal and neonatal factors between hyponatremia group and non-hyponatremia groups

Parameters	Non-hyponatremia group (n = 89)	Hyponatremia group (n = 37)	*P* value
GA at birth (weeks), mean ± SD	32.1 ± 2.7	29.3 ± 3.4	< 0.01
Birth weight (g), mean ± SD	1,550.2 ± 439.3	1001.2 ± 343.6	< 0.01
M:F ratio	1: 1.12	1: 1.08	0.65
5 min AS < 7, No. (%)	28 (31.4)	18 (48.6)	0.03
SGA, No. (%)	24 (26.7)	10 (27.0)	0.97
Oligohydramnious, No. (%)	11 (12.4)	6 (16.2)	0.58
Maternal hypertensive disorders, No. (%)	21 (23.6)	6 (16.2)	0.29
GDM, No. (%)	13 (14.6)	4 (10.8)	0.47
PROM > 18 hr, No. (%)	26 (29.2)	19 (51.3)	< 0.01
Prenatal antibiotics, No. (%)	32 (35.9)	21 (56.7)	< 0.01
Prenatal steroid, No. (%)	69 (77.5)	27 (73.0)	0.47
RDS, No. (%)	11 (12.3)	18 (48.6)	< 0.01
PDA, No. (%)	34 (38.2)	29 (78.4)	< 0.01
Sepsis, No. (%)	8 (9.0)	9 (24.3)	< 0.05
IVH ≥ Gr3, No. (%)	5 (5.6)	5 (13.5)	0.11
Antibiotics use, No. (%)	59 (66.3)	34 (91.9)	< 0.01
BM feeding, No. (%)	29 (32.6)	24 (64.9)	< 0.01
Metabolic acidosis, No. (%)	11 (12.4)	3 (8.1)	0.53
Furosemide use, No. (%)	11 (12.4)	19 (51.4)	< 0.01

GA, gestational age; SD, standard deviation; M: F, male: female; AS, apgar score; SGA, small for gestational age; GDM, gestational diabetes mellitus; PROM, premature rupture of membrane; RDS, respiratory distress syndrome; PDA, persistent ductus arteriosus; IVH, intraventricular hemorrhage; Gr, grade by Volpe; BM, breast milk.

According to the multiple logistic regression analysis, a shorter gestation, a shorter duration of parenteral nutrition, the presence of respiratory distress syndrome, the use of furosemide, and feeding with breast milk were independently associated with the development of hyponatremia (Table 2).

Table 2: Multivariate logistic regression analysis of risk factors of hyponatremia

Variables	Odds ratio	*P* value	95% CI for estimate (OR)	
			Lower	Upper
GA (per week)	0.514	0.000	0.318	0.892
RDS	2.925	0.032	1.431	5.410
Furosemide use	3.081	0.009	2.043	5.804
BM feeding	2.416	0.044	1.522	4.394

GA, gestational age; RDS, respiratory distress syndrome; BM, breast milk.

Discussion

During intrauterine life, the foetus lives in a warm, watery environment where it receives a constant supply of water and electrolytes from the mother. On the contrary, following birth, the neonate must adapt to a relatively cold, dry environment with much wider fluctuations than those experienced in the uterus [8], [9]. Variations in the hydro-electrolytic balance in the preterm neonate of very low weight are extreme due to the immaturity of the different organs. The immature kidney in particular leads to high toxicity caused by fluids: in excess when the supply of water is abundant and scanty when the supply of water is insufficient [10]. An abundant supply of fluids is the cause of generalized oedemas and insufficient lung activity brought about by the increase in interstitial liquid directly or indirectly through maintenance of a patent Botallo duct [11]. On the contrary, the insufficient administration of fluids may lead to hypovolemia, hyperosmolarity, metabolic anomalies

and kidney insufficiency [12]. Since the concentration of sodium in the serum is the main indicator of the water balance in the preterm infant, this group of patients presents a particular frequency of hyponatremia and hypernatremia [13]. Recently, serious sequels associated with hyponatremia and variations in sodium concentration in preterm infants have been reported [13], [14]. Hyponatremia is most frequently caused by an excessive supply of water rather than by a reduced sodium intake, while hypernatremia is most frequently secondary to a reduced supply of water or increased losses of water rather than by a excessive supply of sodium [15]. The questions and controversies in neonatology concern the supply of liquids in the first days of life and the amount of the sodium supplement.

In our study, 29.4% of preterm infants born before 36 weeks of gestation were affected by hyponatremia. Despite the relatively small sample size and limitation of a retrospective study, this is, to our knowledge, the first description of the incidence of hyponatremia in Vietnam. The significant risk factors for hyponatremia were a lower gestational age at birth, the presence of respiratory distress syndrome, furosemide use, and feeding with breast milk. Preterm neonates are at high risk for the development of hyponatremia because of (1) lower glomerular filtration rate, (2) reduced proximal tubular reabsorption of sodium, and (3) increased arginine vasopressin levels in response to illness [16], [17].

Some of the suggested pathophysiological causes of hyponatremia in premature babies are inadequate sodium intake and increased natriuresis, which can cause increased vasopressin. Our risk factor analysis supports these pathophysiological factors as causes of hyponatremia. In preterm infants, the immaturity of the proximal renal tubule can cause the decreased reabsorption of sodium. Numerous factors affecting the proximal tubule can aggravate hyponatremia, including hypoxia, respiratory distress, and the administration of drugs with tubular toxicity. Our study showed that the infants' gestational age at birth and birth weight tended to be lower in the hyponatremia group and that respiratory distress syndrome was a significant risk factor for hyponatremia. Another significant risk factor was furosemide, a well-known diuretic that affects kidney tubules, causing massive natriuresis. Regarding inadequate sodium supplementation, feeding with breast milk were significant risk factors.

In the present study, the incidence of hyponatremia was as high as 29.4%. It will, therefore, be of great importance to clarify the clinical consequences of a low serum sodium level in premature babies. Some preliminary data have already indicated that neonatal sodium deficiency may have unfavorable consequences for later cognitive functions [14], [18]. Furthermore, hyponatremia has been documented to be a risk factor for cerebral palsy in extremely premature babies [19].

In preterm infants, increased natriuresis due to renal tubular immaturity can lead to protracted volume contraction, which can stimulate aldosterone and arginine vasopressin (AVP) release, allowing further water retention and the progression of hyponatremia [20], [21], [22]. The elevation of plasma AVP levels in bronchopulmonary dysplasia (BPD) infants both during the fourth week of life and as a chronic condition has also been reported [23], [24]. Although an impaired renal response to AVP in hyponatremic patients prevents the further worsening of hyponatremia [20], elevated AVP levels in BPD patients can cause pulmonary fluid to accumulate, increasing pulmonary edema; therefore, hyponatremia may be a significant risk factor for BPD.

Postnatal growth retardation related to hyponatremia has also been reported [25]. Sodium is a significant growth factor that stimulates cell proliferation and plays a significant role in protein turnover [26]. NaCl deprivation inhibits growth, which is manifested in reductions in body weight, brain weight, body length, muscle and brain protein and RNA content, and brain lipid content (compared with controls). Subsequent NaCl supplementation restores the growth velocity; however, it does not induce catch-up growth [26].

What does this mean for the practicing clinician? Neonatologists should make every effort to keep serum sodium concentrations in the normal range. Hyponatremia in preterm infants is an iatrogenic complication that should be preventable, because newborns start out life with normal serum sodium concentrations. One practice that needs to be reconsidered how parenteral fluids are being prescribed to the preterm neonate. Current recommendations are to prescribe 5% dextrose in water, only adding sodium after weight loss has been achieved [27]. The reason for this recommendation is the concern that sodium supplementation in the immediate postnatal period will lead to extracellular volume expansion with the development of hypernatremia, worsening respiratory distress, necrotizing enterocolitis, and patent ductus arteriosus [28], [29].

In summary, hyponatremia occurred at a relatively high frequency. This result exemplifies the importance of serum sodium monitoring and supplementation for the correction of hyponatremia, especially if the hyponatremia persists for long periods despite a lack of acute symptoms. Nonetheless, as this was a retrospective study, hyponatremia might be only a marker of disease severity rather than an etiologic factor. Thus, further large cohort studies are needed in this area.

Acknowledgments

The authors are grateful to physicians, administrative staff at Neonatal Intensive Care Unit of Hue Central Hospital for allowing us to undertake this research.

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