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Prevalence and risk factors of dysnatremia in sick newborns admitted in neonatal intensive care unit: a cross-sectional study

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ABSTRACT

Background: The objective of the study was to study the prevalence and various risk factors of dysnatremia in sick newborns admitted in neonatal intensive care unit (NICU).

Methods: Cross sectional study conducted in Paediatric Department of tertiary care hospital from February 2016 to October 2016 which includes 384 neonates admitted to NICU during the study period. After informed consent, detailed history was taken and clinical examination carried out in both cases and controls. Blood investigations were done to diagnose sodium levels in sick neonates. Based on the corrected sodium values, the subjects were classified as having hyponatremia (serum sodium <135 meq/l), hypernatremia (serum sodium >145 meq/l) or normonatremia (serum sodium 135 to 145 meq/l).

Results: The mean (SD) (range) serum sodium in sick newborns measured was 136.72 (6.7) (115-165) meq/l at a median (range) age of 56.97 (1-545) hours. Out of 384 sodium values obtained, 285 (74.2%) were sent on ≤ 3 days, 64 (16.7%) between 4th to the 6th day and 35 (9.1%) were sent on ≥ 7 days. The overall frequency of dysnatremia in 384 sodium values from 384 patients was 142 (37%). Hyponatremia was observed in 117 (30.5%) and hypernatremia in 25 (6.5%) of sodium values. Hyponatremia observed in term, low birth weight, very low birth weight and extremely low birth weight neonates were 16.4%, 25.2%, 67.2% and 100% respectively whereas hypernatremia were 10.1%, 4.6%, 3.4% and 0% respectively. Various risk factors for hyponatremia namely; prematurity, necrotizing enterocolitis, renal failure, birth asphyxia, sepsis, meningitis, vomiting/ nasogastric drainage.

Conclusions: Hyponatremia are common in sick newborns in NICU.

Keywords: Hypernatremia, Hyponatremia, Dysnatremia, Serum sodium

INTRODUCTION

Hyponatremia and hypernatremia are complex clinical problems that occur frequently in newborns admitted to the Neonatal intensive care unit (NICU). The real magnitude of these potentially devastating conditions is less clear. In adults the pathophysiological mechanism of hyponatremia is well documented whereas within the newborn it's less

clear how and when hyponatremia changes cerebral osmotic equilibrium and how much time brain cells required to adapt themselves to the new hypotonic environment.¹

The reported frequency of these disorders is determined by a number of factors, including the definition of hyponatremia and hypernatremia, the frequency of testing,

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the health care setting, and the patient population. Therefore, there is a need for studies in developing countries including India to assess the magnitude of this problem.

The present study discusses the baseline prevalence rates of dysnatremia and various risk factors associated with dysnatremia in sick newborns admitted in NICU.

METHODS

A cross-sectional study design was used. This study was conducted at the Special care baby unit (SCBU), a level II NICU of Bokaro general hospital (BGH), Bokaro Steel City, Jharkhand, during the period from February 2016 to October 2016. Neonates (both term and preterm babies) are admitted and treated following as per standard NICU protocol. During the period of the study, the concentration of serum sodium ions was measured routinely on all sick neonates on admission as the standard of care. A newborn who had abnormal vital signs, color, activity, or feeding pattern at any point of time in neonatal period was considered sick

Inclusion criteria

Sick neonates of both sexes aged 0 to 28 days admitted to Neonatal Unit (SCBU) were included.

Exclusion criteria

Newborns for whom serum sodium could not be measured during their NICU stay were excluded from the study and newborns admitted in SCBU for follow-up observation, any abnormal vital sign after birth but later (within 24 hours) found to be stabilized were excluded from the study.

A total of 384 sick neonates aged 0-28 days who met the inclusion criteria were included in the study. Written Informed consent was obtained from the mother/caregiver of eligible neonate using an informed consent form. A detailed history was taken regarding birth and obstetric history, gestational age at delivery, feeding if given, any presenting complaints, and various risk factors for dysnatremia namely; prematurity, necrotizing enterocolitis, renal failure, birth asphyxia, sepsis, meningitis, vomiting/ nasogastric drainage, and treatment given at the time of sodium sampling which includes radiant warmer and phototherapy with their duration and recorded on a predesigned proforma. Radiant warmer and phototherapy were considered as a risk factor for hyponatremia for those if they were administered within 24 hours of sampling.

A complete physical examination especially for signs of dehydration, edema, skin pigmentation, ambiguous genitalia was performed. All subjects were followed for the period of hospital stay to study their outcome with respect to survival/neurological sequel. Serum sodium was

repeated by the attending physician during follow-up when clinically indicated. Clinical indication included clinical features indicative of hyponatremia such as seizures, irritability, lethargy, abnormal weight changes; values were also repeated for monitoring response to therapy of hyponatremia. Hyponatremia was managed using standard guidelines.² Associated conditions affecting the babies were managed by the treating physician using standard guidelines. Fluid management of neonates in NICU is done according to standard protocol.³ Babies who had more than one abnormal serum sodium reading were considered to have separate episodes if there was at least one available report of normal serum sodium in the intervening period.

Approximately 3 ml of blood was drawn using the aseptic technique by peripheral venous phlebotomy. Approximately 1 ml blood was transferred to serum separator vials for measuring serum sodium level. Remaining 2 ml blood for sugar estimation was transferred to sodium fluoride vials.

Depending upon serum sodium levels, they were classified as hyponatremia (serum sodium <135 mmol/l), normonatremia (serum sodium between 135 to 145 mmol/l) and hypernatremia (serum sodium >145 mmol/l). Ethical approval was taken from ethical committee.

Measurement of serum sodium level

Serum sodium levels were analyzed in the central laboratory using an Olympus AU 640^{TM} discrete chemistry analyzer (Beckman Coulter India Pvt. Ltd.).

Statistical analysis

Data collected during the study was analyzed using the IBM Statistical package for social sciences (SPSS) StatisticsTM version 20 software. The overall proportion of dysnatremia as well as hypo- and hypernatremia were calculated from among the serum sodium values assessed. The unadjusted odds ratio was calculated for individual risk factors of hyponatremia, using Pearson Chi-square test or Fischer's exact test as appropriate, to define significant risk factors. The adjusted odds ratio was then calculated for these risk factors using logistic regression statistics. Significance was defined at a p<0.05.

RESULTS

A total of 384 neonates were recruited in the study; of these 144 neonates were admitted inborn neonates, while 240 were transferred or referred from other health facilities (out-born). Out of 384 subjects enrolled, 264 (68.8%) were male while 120 (31.3%) were female. There were 164 (42.7%) preterm, 220 (57.3%) term and 0 (0%) post-term babies. Mode of delivery was normal vaginal in 287 (74.7%) and lower segment caesarean section in 97 (25.3%).

Table 1: Various risk factors of hyponatremia.

Risk factors		Hyponatremia (%)	Hypernatremia (%)	Total (%)
Prematurity	Present	75 (50)	75 (50)	150 (100)
	Absent	42 (17.9)	192 (82.1)	234 (100)
	Total	117 (30.5)	267 (69.5)	384 (100)
Vomiting	Present	20 (76.9)	6 (23.1)	26 (100)
	Absent	97 (27.1)	261 (72.9)	358 (100)
	Total	117 (30.5)	267 (69.5)	384 (100)
Sepsis	Present	55 (41.0)	79 (59.0)	134 (100)
	Absent	62 (24.8)	188 (75.2)	250 (100)
	Total	117 (30.5)	267 (69.5)	384 (100)
Necrotising enterocolitis	Present	14 (58.3)	10 (41.7)	24 (100)
	Absent	103 (28.6)	257 (71.4)	360 (100)
	Total	117 (30.5)	267 (60.5)	384 (100)
Renal failure	Present	10 (52.6)	9 (47.4)	19 (100)
	Absent	107 (29.3)	258 (70.7)	365 (100)
	Total	117 (30.5)	267 (69.5)	384 (100)
Meningitis	Present	06 (40)	09 (60)	15 (100)
	Absent	111 (30.1)	258 (69.9)	369 (100)
	Total	117 (30.5)	267 (69.5)	384 (100)
Birth asphyxia	Present	49 (40.2)	73 (59.8)	122 (100)
	Absent	68 (25.9)	194 (74.1)	267 (69.5)
	Total	117 (30.5)	262 (100)	384 (100)

Table 2: Logistic regression for hyponatremia.

Regression variables	p values	Odds	95% CI for odds ratio	
		ratio (Exp (B))	Lower	Upper
Prematurity	0.000	4.807	2.908	7.947
Vomiting/ nasogastric aspiration	0.012	4.336	1.373	13.697
Clinical sepsis	0.046	1.766	1.010	3.090
NEC	0.731	1.215	0.400	3.695
Meningitis	0.525	0.621	0.143	2.693
Birth asphyxia	0.001	3.432	1.701	6.925
Renal failure	0.065	2.893	0.936	8.943

The mean (SD) weight and gestational age of the study group was 2.175 (0.697) kg and 38.44 (1.98) weeks respectively. The median (range) of age at assessment of serum sodium was 56.97 (1- 545) hours. Out of 384 subjects, 151 (39.3%) were low birth weight, 64 (16.7%) were very low birth weight and 10 (2.6%) were extremely low birth weight.

A total of 384 serum sodium values from 384 sick neonates were collected, with a minimum of one from each. Out of 384 neonates, single sodium value was obtained from 352 neonates, two readings were obtained from 31 neonates and three readings from 1 neonate .In those cases, where repeated serum sodium estimation was done, only the most deranged level of sodium was considered for the study. Out of 384 sodium values obtained, 285 (74.2%) were sent on \leq 3 days, 64 (16.7%) between 4th to the 6th day and 35 (9.1%) were sent on \geq 7 days.

The overall frequency of dysnatremia in 384 sodium values from 384 patients was 142 (37%). Hyponatremia was observed in 117 (30.5%) and hypernatremia in 25 (6.5%) of sodium values. Dysnatremia on day 1 of life (n=219) had 39.3% prevalence of which hyponatremia was 37% and hypernatremia was 2.3%. Dysnatremia prevalence on day 2 of life (n=31) was 29% of which hyponatremia was 25.8% and hypernatremia was 3.3%. Prevalence of dysnatremia among day 3 of life (n=35) sodium values was 20% of which 11.4% was hyponatremia and 8.6% was hypernatremia.

The prevalence of hyponatremia from 64 serum sodium values obtained from 64 VLBW neonates (<1.5 kg) was 67.2%. Out of 10 ELBW neonates (<1.0 kg), all neonates had hyponatremia (100%) and none had hypernatremia.

The mean (S.D) (range) serum sodium in sick newborns measured was 136.72 (6.7) (115-165) meq/l at a median age of 56.97 hours. The mean (SD) sodium of all sick newborns on day 1 of life was 135.37 (6.02) meq/l. Mean (SD) sodium in hyponatremic patients on day 1 of life was 129.11 (4.3) meq/l, mean (SD) serum sodium in hypernatremic neonates on day 1 of life was 148.6 (3.7) meq/l. Mean (SD) (range) serum sodium in preterm neonate on day 1 of life was 133.46±5.64 (118-155) meq/l. Out of 117 serum sodium values of hyponatremia, 20 values were <125 meq/l. There were 7 other sodium values of 125 meq/l.

Risk factors for hyponatremia

Prematurity

Of the 150 serum sodium values obtained from 150 preterm babies, 75 (50%) were hyponatremic in contrast the figure was 42 (17.9%) from 234 sodium values obtained from the remaining 234 babies and this difference was found.

Vomiting/nasogastric drainage

Test results of hyponatremia among babies with vomiting/nasogastric drainage were much much higher than rest of the neonates, 20/26 (76.9%) versus 97/358 (27.1%), and this difference was found to be statistically significant.

Sepsis

Of the 134 serum sodium values from neonates with sepsis, 55 (41.0%) were hyponatremic and 62 (24.8 %) of 250 serum sodium values from neonates without sepsis had hyponatremia. On chi-square test, the association of sepsis in the causation of hyponatremia was considered to be statistically significant with a p value of 0.015.

Necrotizing enterocolitis

Test results of hyponatremia among neonates with necrotizing enterocolitis were higher as compared to neonates without necrotizing enterocolitis, 14/24 (58.3%) versus 103/360 (28.6%). This difference was statistically not significant. p=0.084 odds ratio (95% CI) 3.493 (1.503-8.116).

Renal failure

Though test results of hyponatremia were higher in neonates with renal failure than neonates without renal failure, 10/30 (52.6%) versus 107/365 (29.3%), this difference was considered to be statistically significant. Odds ratio (95% CI) 2.679 (1.059- 6.779).

Meningitis

Out of 15, 6 (40%) sodium values of newborns with meningitis were of hyponatremia while 111 (30.1%) of

369 serum sodium values of neonates without meningitis were of hyponatremia. This difference was not statistically significant.

Present

Birth asphyxia

Of 122 values of serum sodium of neonates with Birth asphyxia, 49 (40.2%) showed hyponatremia while 68 (25.9%) of 266 values from neonates without birth asphyxia showed hyponatremia. This difference was found to be statistically significant. OR of 3.432 (95% C I=1.701-6.925) p=0.

DISCUSSION

Hyponatremia and hypernatremia are undoubtedly complex clinical problems that occur frequently in newborns admitted to the NICU. The real magnitude of these potentially devastating conditions is less clear. The reported frequency of these disorders is determined by a number of factors, including the definition of hyponatremia and hypernatremia, the frequency of testing, the health care setting, and the patient population.³

There have been several reports of the adverse impact of changes in serum sodium levels on neurologic outcomes for preterm neonates.^{4,5}

Surprisingly almost all the studies regarding dysnatremia and their effect are from developed countries and there are few studies representing developing countries including India.

Therefore, there is a need for studies in developing countries including India to assess the magnitude of this problem. The present study discusses the baseline prevalence rates of dysnatremia and various risk factors associated with dysnatremia in sick newborns admitted in NICU of Bokaro General Hospital, Bokaro Steel City, Jharkhand, India.

Although there are increasing reports of dysnatremia in newborns in recent years in the form of case reviews, case series, there are very few studies conducted on large populations to know the prevalence of the condition. 6-10 In our study we found the prevalence of dysnatremia to be 37% in sick newborns admitted to NICU.

In our study we found the prevalence of hyponatremia to be 30.5% in sick newborns which were comparable to other studies which have shown the frequency of hyponatremia in very ill newborns to vary from 25-65%.³

In our study we found the prevalence of hyponatremia in VLBW neonates to be 67.20% which is slightly higher than that observed by Kloiber et al,who conducted a retrospective cohort study at St. Luke's Hospital in Kansas city, USA, and found incidence of hyponatremia in very

low birth weight infants admitted to intensive care nursery to be 62.5%, which is comparable to their study. ¹¹ In another cross-sectional study by Moss et al on infants with less than 1.5 kg birth weight admitted in NICU at University Teaching Hospital, Lusaka, Zambia, it was observed that incidence of hyponatremia was 51%, which is less than that of our study. ¹² Al-Dahhan et al found hyponatremia, defined as plasma sodium less than 130 to be present in 23 out 30 (76%) of VLBW babies. ¹³ However, this study was conducted on otherwise healthy very low birth weight infants fed on commercial formula.

In our study prevalence of hyponatremia in extremely low birth weight neonates was 100% which is much higher than 33.3% found by Takahashi et al who retrospectively analyzed water and electrolyte balance in 100 ELBW babies.¹⁴

However, in our study total numbers of extremely low birth babies were only 10. The prevalence of hyponatremia in term neonates admitted to NICU in our study was 16.40%. A previous study done by Kumar et al on healthy neonates with neonatal hyperbilirubinemia receiving phototherapy, found the prevalence of hyponatremia in term babies to be 3.10%. This difference was plausibly because neonates included in our study had other comorbid conditions predisposing them to hyponatremia.

The prevalence of hypernatremia in our study was 6.5%. Prevalence of hypernatremia has been assessed by many authors. However, this has been noted in healthy and exclusively breastfed infants. Gawlowski et al studied the incidence of hypernatremia in preterm neonates born less than 27 weeks gestation and found it to be 69.7%. However, in our study, only seven neonates had a gestation of <28 weeks and all seven were hyponatremic (100%).

Risk factors of hyponatremia

Prematurity

Premature birth requires a sudden adaptation to a gaseous environment with a low humidity, and in the first week of life, the premature infant presents a physiologically negative sodium and water balance caused by contraction of extracellular fluid. Preterm neonates have the limited tubular capacity to reabsorb sodium and hence increased urinary losses. There is a poor response to the antidiuretic hormone in the distal convoluted tubule due both to deficient secretion and reduced tubular sensitivity. The reabsorption of sodium at the intestinal level is also reduced. Thus preterm newborns are at risk for developing hyponatremia. These facts are endorsed by results of our wherein we observed the prevalence hyponatremia to be higher among preterm sick neonates (50%) when compared to term babies (16.4%). The difference was statistically significant with a p<0.001. These results are in accordance with Al-Dahhan et al who found that the sodium balance was negative in 100% of infants of less than 30 weeks gestation, in 70% at 30-32 weeks, in 46% at 33-35 weeks and in 0% of more than 36 weeks and the incidence of hyponatremia closely paralleled that of negative sodium balance. However, this study was conducted on healthy neonates.

Renal failure

Acute or advanced renal insufficiency is also a risk factor for the hypervolemic type of hyponatremia. In our study also 52.6% of sodium values of newborns with renal failure were hyponatremic as compared to 29.3% of newborns without renal failure. This difference was found to be statistical significance (p<0.05).

Necrotizing enterocolitis

Necrotizing enterocolitis is a cause of hypovolemic hyponatremia due to the third space losses.² In our study also hyponatremic results were more frequent in newborns with necrotizing enterocolitis (58.3%) as compared to those without necrotizing enterocolitis (28.6%) p>0.05.

Vomiting/nasogastric drainage

Vomiting also causes hypovolemic hyponatremia due to gastrointestinal losses. In our study also hyponatremic results were more frequent in newborns with vomiting/nasogastric drainage (76.9%) as compared to those without vomiting/nasogastric drainage (27.1%). This difference was statistically significant with a p<0.001.

Birth asphyxia

The frequency of hyponatremia was higher among babies with birth asphyxia (40.2%) as compared to babies without birth asphyxia (25.9%). This difference was also statistically significant with a p=0.001.

Meningitis

In our study we find hyponatremia to be more common in neonates with meningitis. About 40% of sodium values of newborns with meningitis showed hyponatremia while 30.1% of sodium values of newborns without meningitis showed hyponatremia. Low sodium concentration in newborns with brain injury is often attributed to SIADH, excessive release of AVP in brain injury being ascribed to a damage of the osmoreceptors leading to a release of AVP even at lower serum osmolarity.

Clinical sepsis

In our study, we find hyponatremia to be more common in neonates with sepsis as compared to neonates without sepsis. Of neonates with sepsis, 41.0% of sodium values were hyponatremic, while 24.8% of sodium values of neonates without sepsis. This difference was statistically significant (p<0.05).

Logistic regression test for risk factors for hyponatremia

A multivariable logistic regression test demonstrated that prematurity, sepsis, vomiting/ nasogastric drainage and birth asphyxia were statistically significant risk factors for hyponatremia. It indicates that hyponatremia was 5 times more common in premature babies as compared to mature babies (adjusted OR=4.807, p<0.001). Hyponatremia in clinical sepsis was 2 times more commonly found as compared to neonates without sepsis (adjusted OR=1.766, p=0.046). Hyponatremia associated with neonates who had birth asphyxia was 3 times more common as compared to neonates without birth asphyxia (adjusted OR=3.432, p=0.001). Hyponatremia was also 4 times more commonly seen in neonates with vomiting/ nasogastric drainage (adjusted OR=4.336, p=0.012). Other variables NEC, renal failure, and meningitis did not show significant association with hyponatremia.

Risk factor for hypernatremia

Radiant warmer and phototherapy are important causes of increase in insensible water losses and resulting hypernatremia. In our study, we did not find hypernatremia to be more common in neonates exposed to radiant warmer. This was probably due to strict fluid management is done on sick neonates receiving radiant warmer based on 24 hourly monitoring of weight changes.

Duration of phototherapy

Hypernatremia was more common with neonates exposed to phototherapy for >24 hours (14.5%) as compared to neonates who were not exposed to phototherapy (1.9%), or neonates exposed to phototherapy less than 24 hours (6.2%) and this difference was statistically significant with p value 0.004 (p<0.05). Kumar et al studied serum sodium changes in neonates receiving phototherapy for neonatal hyperbilirubinemia, observed that mean serum sodium levels were significantly decreased after phototherapy but it was more common in preterm and low birth weight babies, but our result showed that mean serum sodium levels were significantly increased after phototherapy. ¹⁰

Outcome

Survival

In our study, we found that groups of neonates who expired had a higher frequency of dysnatremia but independently sodium status does not seem to affect the survival in this cohort. This is plausibly because all these babies had other co-morbid conditions. Although the numbers are too small to draw a definite conclusion, out of 20 neonates who had serum sodium values less than 125 meq/l, 13 expired. Out of 3 neonates who had serum sodium values less than 120 meq/l, 1 expired. These findings are comparable with the study of Sherlock et al who showed an exponential increase in mortality when the serum sodium concentration falls below 120 meq/l peaking at 50% when

the serum sodium concentration falls below 115 meq/l. ¹⁶ In another study, Guarner et al showed, sodium levels of ≤120 mmol/l and ≥170 mmol/l have increased mortality in sick newborns which are also comparable to our findings. ¹⁷

Neurological sequelae

We found no relation of sodium status (both hyponatremia and hypernatremia) to the neurological outcome at discharge. Murphy et al found that hyponatremia was a factor associated with increased risk of cerebral palsy after adjustment for gestational age and prenatal and intrapartum risk factors. Baraton et al studied the impact of changes in serum sodium level on two years follow up, wherein neurological outcomes for preterm neonates was observed, and found that large changes in serum sodium levels were significantly associated with risk of impaired functional outcomes after adjustment for gestational age and perinatal and neonatal hospitalization characteristics. 19

Limitations

This study was limited by a number of sodium values obtained beyond the third day of life. Therefore, factors which come into play with longer duration of stay in neonatal intensive care unit example- radiant warmer and phototherapy exposure could be studied in a limited number of patients. Since the study was done at the tertiary care center of Jharkhand, only high-risk patients sent to the hospital were enrolled and this may not be a true reflection of the general population. It is important to note that many other factors that can have an effect on serum sodium levels in premature neonates, such as maternal exposure to steroids, diuretics and neonatal exposure phenobarbitone, soda bicarbonate, mannitol etc were not considered for the study.

CONCLUSION

From the study findings, the baseline prevalence of hyponatremia and hypernatremia in NICU at Bokaro General Hospital among sick neonates was found to be 30.5% and 6.5% respectively, and the prevalence rate of hyponatremia was found to be highest among the neonates less than 1.5 kg of weight. It is reasonable to conclude that hyponatremia are common in sick newborns in NICU.

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Ethical approval: The study was approved by the

Institutional Ethics Committee

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