East African Medical Journal Vol. 79 No. 3 March 2002
HYPONATRAEMIA IN VERY LOW BIRTH WEIGHT INFANTS
D.N. Ndwiga MBChB, Senior Resident/Postgraduate Student, F.N. Were, MBChB, MMed, FNIC. Lecturer and R.N. Musoke, MBChB, MMed, Associate Professor. Department of Paediatrics and Child Health, College of Health Sciences, University of Nairobi, P.O. Box 19676, Nairobi, Kenya.

Request for reprints to: Dr. F. N. Were, Department of Paediatrics and Child Health, College of Health Sciences, University of Nairobi, P.O. Box 19676, Nairobi, Kenya.

HYPONATRAEMIA IN VERY LOW BIRTH WEIGHT INFANTS

D.N. NDWIGA, F.N. WERE and R.N. MUSOKE

ABSTRACT

Background: **Infants less than 1500 grams at birth have been demonstrated to be particularly prone to development of low levels of serum sodium often leading to increased early neonatal morbidity and mortality. No local study has been done to quantify this problem among sick newborns. Studies elsewhere demonstrate a high incidence of hyponatraemia among such preterms.**

Objective: **To evaluate the influence of infant early neonatal morbidity on serum sodium levels and justify regular monitoring and supplementation.**

Design: **Comparative cohort study.**

Setting: **Newborn Unit, Kenyatta National Hospital, Nairobi.**

Subjects: **Fifty six very low birth weight (1000-1500 grams at birth) infants during their first week of life. Half of them were designated as cases in view of having various early neonatal illnesses. The remaining 28 being clinically stable were taken as controls. These two groups had comparable birthweights, sex distribution and gestational ages. Their sodium intakes were also similar during the first week of life.**

Results: **The sick infants (cases) had persistently low serum sodium (mean of 120 mmols/L) throughout the first week while among the healthy infants (controls) a sequential increase from 127 to 133 mmol/l, (mean values) was observed during the same period. The difference registered on day seven (133 versus 120) was statistically significant (p= 0.02). Using a cut off point of 130 mmol/L to define hyponatraemia the proportion of infants with hyponatraemia, which was similar at the beginning became higher among the cases for the rest of the week with the largest disparity observed on the seventh day (75% versus 23%, p=0.007). Urinary sodium losses as measured by Fractional Sodium Excretion were also initially similar between the two groups but later became higher among the cases (4.96 versus 3.5 p=0.08).**

Conclusion: **Very low birth weight infants who are ill have lower serum sodium and are more likely to develop significant hyponatraemia than their healthy counterparts during the first week of life. Standard care of these sick infants must therefore routinely include regular monitoring of serum sodium and its correction if found to be low.**

INTRODUCTION

Sodium is the most osmotically active solute responsible for the maintenance of both intra and extra vascular fluid volumes. It is also of pivotal importance in the processes of cell membrane polarisation vital for many biological functions. Its homeostasis is therefore essential for life.

Normal term infants seem to conserve body sodium even in the presence of wide ranges of salt intakes(1,2). Contrastingly, premature infants have deficient conservation mechanisms with predominant urinary wastage disproportionate with both intake and body requirements(3-9). These imbalances are usually more pronounced with smaller and less mature infants(2).

Studies done in stable very low birth weight (VLBW) infants (birth weight between 1000 and 1500 grams) have reported up to 30% rates of hyponatraemia(6,7). The only local study reported no hyponatraemia among infants of similar gestation as the current one(10). In Ayisi's series however only infants older than one week and predominantly fed on mothers milk were selected. They were thought to have had adequate sodium intake from their mother's milk.

Sick pre-term babies develop hyponatraemia much more often than their healthy counterparts(1,2). They also tend to have more severe degrees of the clinical syndromes of hyponatraemia. These include convulsions, intraventricular bleeds, poor growth and pulmonary oedema(2). Engelke found hyponatraemia in 50% of 17 sick newborns weighing less than 1200 grams at birth(11). Rees described an even higher incidence of 80% in a comparable group of patients(12). Engelke and Rees also observed excessive urinary sodium losses accompanying the low serum sodium especially after the first three days of life. The mechanisms by which neonatal illnesses reduce serum sodium include enhancing urinary losses in

the late phase due to defective renal tubular conservation mechanisms(13-17) and the increased occurrence of the syndrome of Inappropriate Anti-Diuretic Hormone release during the first three days(18). The latter brings about dilutional hyponatraemia.

The frequency of significant hyponatraemia in sick VLBW infants at our centre has not been reported before. Our objective was to determine the influence of early neonatal morbidity on sodium balance in Very Low Birth Weight infants during their first week of life.

MATERIALS AND METHODS

The study was undertaken at the Kenyatta National Hospital, which is also the University of Nairobi's teaching facility between February and May 1998. It was a cohort survey involving two groups of infants whose birth weights were between 1000 grams and 1500 grams. One cohort, the cases consisted of those found to have some early neonatal morbidity such as respiratory distress syndrome, infection, jaundice and asphyxia. The other group was made up of healthy infants. Only babies appropriate for gestational ages as assessed by Ballard's method were eligible for the study(19). The subjects were recruited consecutively upon completion of 24 hours and allocated to either group. The required sample was 28 per group based on the appropriate statistical formula for comparison of cohorts. We used the 30% prevalence of hyponatraemia in healthy very low birth weight infants observed by Roy and Day(6,7) and 70% for the sick babies. The latter was computed by combining the Engelke and Rees studies(11,12). The level of significance was set at 0.05.

Clinical procedure: Birth weight was measured to the nearest gram. Gestational age was computed from the menstrual history and confirmed by Jeanne Balland clinical scoring(19). The patients were otherwise managed as per the usual protocol of the unit. Whenever possible they were fed on their mother's milk. Otherwise intravenous crystalloids containing 3 mmol/kg/day of elemental sodium were used till the babies were stable enough for tube feeds.

Laboratory procedures: Blood and urine samples were collected on days 2, 3, 5 and 7 for assays of sodium and creatinine. The sodium assays were done using the Ion Selective Electrode Analyzer method in the University biochemistry laboratory. A total of one millilitre of blood was drawn at each sampling. Serum creatinine was determined by the Jaffe Picric Acid method. Fractional Urinary Excretion of sodium (FeNa) was then computed from the formula FeNa=(UNa/SNa) x (SCr/Ucr) x 100. (UNa = urine sodium, SNa = serum sodium, UCr =urine creatinine and SCr =serum creatinine). Milk was obtained by pooling 1 millilitre from each of the feeds of the day and analysed for sodium content by the same assay methods described above.

Consent: Approval was obtained from the Ethical Committee of the Hospital. The parents of the infants were required to give written consent.

Data analysis: Summarisation and tabulation was done and proportions computed. Statistical validation employed the Z and $\chi 2$ tests for comparing proportions, the Student's t-test for comparing group means of independent samples and the paired t-test for measuring differences within the groups. The calculations were done using the Epidemiological Information Statistical programme.

RESULTS

Baseline data including birth weight, gestation, sex ratio and sodium intake were compared, between the two groups in order to control the influence of those variables considered possible confounders (Table 1).

Table 1

Comparison of baseline parameters

Variable	Cases (Sick Babies)	Controls (Healthy Babies)	P value
Sex ratio (M:F)	1.1 :1	1.1 :1	0.82*
Mean birth weight (grams)	1282	1296	0.73#
Mean gestation (weeks)	29.6	30.1	0.25#
Mean sodium intake (mmols/kg/day)	3.5	2.9	0.21#

* Chi-square distribution test. # Student's t-test. The sex ratio was actually similar in the two groups. Some marginal numerical differences were observed for the rest of the parameters but none attained statistical significance.

Serum sodium levels: The serum sodium levels on days 2, 3, 5 and 7 were determined for each subject. The mean sodium levels were lower in the sick newborns (cases) at all ages with the peak difference observed on day 7 (120 mmol/L in the sick and 133 mmol/L among the well babies). This last difference was statistically significant. Well VLBW babies tend to have higher serum sodium levels than the sick ones (Table 2).

Hyponatraemia: Using serum sodium level of 130 mmol/l as the cut-off point for defining hyponatraemia, the two groups were compared to determine the differential occurrence of hyponatraemia (Table 3).

The two groups had the same proportion of infants with hyponatraemia at recruitment (day 2). In the latter days however, this proportion remained higher among the sick infants (cases) with the highest disparity observed on day 7 (75% versus 23%, p=0.007). Sick VLBW babies are more likely to develop hyponatraemia than their stable counterparts, especially after seven days.

Table 2

Mean sodium levels

Status of pre-term infant	Day 2		Day 3		Day 5		Day 7	
	No.	Mean (SD)	No.	Mean (SD)	No.	Mean (SD)	No.	Mean (SD)
Sick (cases)	28	120.83 (18.75)	26	127.69 (18.91)	19	120.86 (18.94)	15	120.67 (14.58)
Healthy (controls)	28	127.10 (11.49)	20	131.42 (13.31)	18	127.48 (17.94)	16	133.69 (13.68)
* p value		0.08		0.47		0.30		0.02

* Student's t-test.

Table 3

Levels of hyponatraemia (proportion with serum sodium below 130 mmol/litre)

Status of infant	Day 2		Day 3		Day 5		Day 7	
	No.	% hyponat.	No.	% hyponat.	No.	% hyponat.	No.	% hyponat.
Sick infants (Cases)	28	60.9	26	46.2	19	68.4	15	75.0
Healthy infants (Controls)	28	61.5	20	36.8	18	50.0	16	23.1
# P value		0.6		0.38		0.22		0.007

The Z test for proportions was used.

Table 4

Fractional urinary sodium excretions

Status of infant	Day 2		Day 3		Day 5		Day 7	
	No.	Mean (SD)	No.	Mean (SD)	No.	Mean (SD)	No.	Mean (SD)
Sick infants (Cases)	28	4.37 (2.18)	26	3.20 (2.78)	19	4.30 (2.77)	15	4.96 (2.10)
Well infants (Controls)	28	4.88 (1.64)	20	3.52 (1.63)	18	4.18 (2.68)	16	3.50 (1.25)
*P values		0.24		0.36		0.46		0.08

Sodium losses in urine: To ascertain one of the probable explanations for the low sodium levels and occurrence of hyponatraemia the urinary sodium losses were estimated and compared between the two groups (Table 4).

The mean fractional sodium excretion in urine was similar between the two groups during the first five days. On the seventh day, it was higher among the sick babies (4.96 versus 3.5, p=0.08). Sick VLBW infants appear to pass more sodium in their urine by the end of their first week of life than their healthy counterparts. Although, this difference was not statistically significant it may suggest a trend continuing into the second week of life.

DISCUSSION

This study reveals the presence of a negative sodium balance in a considerable number of VLBW babies during their first week of life. The infants deemed well had mean serum sodium levels between 127 and 130 mmol/L during their first five days of life. The sick babies had even lower levels in the same period (120 mmol/L). It is apparent that many infants survive the first five days at this centre with lower than normal levels of serum sodium. The likely mechanisms of this low serum sodium are the inter-compartmental shift of sodium and water(8,9,20) and the syndrome of anti-diuretic hormone release(18) that are prevalent at this age. As these two factors are usually exaggerated by prematurity and concurrent illnesses it is not surprising that the sick infants had lower levels of serum sodium than the healthy ones. This finding has been observed by other workers(11,12). The management of low serum sodium at this stage should consist of restricting fluids to reduce the fluid surplus brought about by these mechanisms. The routine fluid intake for VLBW infants in our unit is 80 millilitres per kilogram on day one increasing by 20 millilitres per kilogram every subsequent day through the first week of life. No effort is focussed on identifying individual needs of different patients. There is no routine fluid and electrolyte monitoring. This must in part explain these low sodium levels that are most likely related to the effects of dilution.

The mean serum sodium was significantly higher (p=0.03) in the stable babies at the end of the first week. At this stage the contribution of excessive urinary losses was beginning to prevail and a higher fractional sodium excretion (though not statistically significant) among the sick infants was noted. Engelke(11), Broberger(21) and Rees (12) also observed excessive urine losses of sodium among VLBW infants, which appeared to be worsened by concurrent illness. These earlier studies identified an imbalance between intake and urine losses of sodium to be the principle cause of low serum sodium after the first three days of life(11,12,21). Our results are in agreement with these studies. We have also demonstrated that with fixed sodium intakes sick babies are unable to establish and maintain normal serum sodium to the same degree as the healthy ones.

There is a high occurrence of hyponatraemia (defined as any infant with serum sodium lower than 130 mmol/L) in this population. Sixty one per cent of both groups of infants were affected at the beginning of the study. The healthy group however showed a gradual but steady improvement with the rate coming down to 23% by day seven. This figure of 23% is nevertheless still much higher

than the zero per cent reported among the same category of infants in 1990 at this unit(10). This earlier study was however confined to infants one week or older who were exclusively fed on breast milk. Many of our well babies remained on some intravenous crystalloids throughout the study.

The two groups had similar rates of hyponatraemia on the second day of life (61%). We subsequently observed a steady increase among the sick infants (while the well babies were improving) through the week. By day seven 75% of the sick infants had hyponatraemia compared to only 23% of the healthy ones. We could only find such figures in old literature; 50% by Engelke in 1978(11) and up to 80% by Rees in 1984(12). This was at the beginning of the prolific development of neonatal intensive care that took place in the final quarter of the twentieth Century. We are therefore, still at the stage that prevailed before the modern era of intensive biochemical monitoring of sick newborns had been perfected. Aetiologically this late hyponatraemia must have been due to the high urine losses of sodium in the background of inadequate intake. Similar findings have been reported(11,12). The sodium intake in this study was constant at 3-4 mmol/kg/day throughout the week for all the subjects. This is the amount theoretically recommended for well babies though even they often need more(22,23). Sick VLBW infants have very diverse and unpredictable sodium requirements often as high as 10 mmol/kg/day or more especially towards the end of their first week of life and beyond(24).

CONCLUSION

Both early and late hyponatraemia are still very common among VLBW infants in our centre especially when they are ill. Judicious management of fluid balance in the first few days and supplementation of sodium later to sick VLBW infants is recommended.

REFERENCES

1. Paul L., Carthy M.C.. Body content of sodium; Nelsons textbook of Paediatrics 14th Edition, W.B. Saunders, Philadelphia; 1992 .173
2. Avery G.A. and Fletcher A.B.. Nutrition in the newborn. Gordon Avery's textbook of neonatology 3rd Edition 1987: JB Lippincott, Philadelphia, 1987: 1189.
3. Levinsky N.G. Fluid and electrolytes. Harrison's Principals of Internal Medicine 13th Edition, McGraw-Hill Inc, New York: 1994: 242-248.
4. Engelke W.D. Evaluation of renal function in the neonate. *Paediat. Clin. N. Amer.* 1986; **33**:135-136.
5. Spitzer A. The role of the kidney in sodium homeostasis during maturation. *Kidney Intern.* 1982; **21**:539-545.
6. Day G.M., Raddle I.C., Baflle J.W. and Chance G.E. Electrolyte abnormalities in very low birth weight infants. *Paediat. Res.* 1976; **10**:522-526.
7. Roy R.N., Chance G.E., Raddle I.C., Hill D.E., Willis D.M. and Sheepers, J. Late hyponatraemia in very low birth weight infants, *Paediat. Res.* 1976; **10**:526-531.
8. Kagan B.M., Stanicova V., Felix N.S., Hodgman J. and Kalman. Body composition of premature infants. *Amer. J. Clin. Nutr.* 1972; **25**:1152-1160.
9. Friis-Hansen B. Body water compartments in children; changes during growth. *Paediat.* 1961; **28**:169-176.
10. Ayisi RK., Mbiti, M.J.N., Musoke, R.N. and Orinda, D.A.O. The effect of sodium supplementation on sodium homeostasis in very low birth weight infants fed on own mothers milk. *East Afr. Med. J.* 1992; **69**:591-595.
11. Engelke S.C., Shah B.L. Vasan U. and Raye J.R. Sodium balance in very low birth weight infants. *J. Paediat.* 1978; **93**:837-841
12. Rees L., Shaw J.C., Brook G.D. and Forsling M.L. Hyponatraemia in the first week of life in preterm infants. *Arch. Dis. Child.* 1984; **59**:423-429.
13. Sinclair J.C., Driscoll J.M. Heird W.C. and Winters RW. Supportive management of the sick neonate. *Paediat. Clin. N. Amer.* 1970; **17**:863-875.
14. Proesmans W., Geussens H., Corbeel L. and Eeckels R. Pseudo aldosteronism. *Amer. J. Dis. Child.* 1973; **126**:510-518.
15. Rosler A., Gazit E., Theodor R., Biochins, H. and Robinowitz D. Salt wastage, raised plasma rennin and normal or high plasma aldosteronism. *Lancet* 1973; 1:959-966.
16. Aperia A. and Zetlestrom R. Renal control of fluid and homeostasis in the newborn infant. *Perinatology.* 1982; **9**:523-533.
17. Aperia S., Broberger O. and Zetlestrom R. Development study of renal salt load in pre-term infants. *Acta. Paediat. Scand.* 1974; **63**:517-524.
18. Robertson N.C.R. Fluid and electrolyte balance. A manual of neonatal intensive care, 3rd edition, Edward Arnold, London, pp 37-46, 1993.
19. Ballard J., Norak K.C. and Driver M. A simplified score for assessment of foetal maturity on newly born infants. *J. Paediat.* 1979; **95**:769-774.
20. Kerpel-Fronius E., Heim T. and Sulyok E. The development of the renal acidifying process and relation to acidosis in LBW infants. *Biol. Neonate,* 1970; **15** :156-164.
21. Broherger U. and Aperia A. Renal function in infants with hyperbilirubinaemia. *Acta Paediat. Scand.* 1979; **68**:75-79.
22. Klaus M.H. and Fanaroff A.A. Care of the High Risk Neonate 3rd edition. W.B. Saunders, Philadelphia. Pp 410, 1986.
23. Al-Dahan H., Haycock G.B. and Nochols B. Sodium homeostasis in the term and pre-term neonates; the effects of supplementation. *Arch. Dis. Child.* 1984; **59**:945-950.
24. Babson H.G. Feeding the low birth weight infants. *J. Paediat.* 1971; **79**:694-701.