RA Publications
JMST
Journal of Medical Science & Technology

Original Article Open Access

Aminophylline loading dose and serum sodium ions in premature neonates admitted to neonatal intensive care unit, at the university teaching hospital, Lusaka, Zambia.

Mr MukoshaMoses, Msc Pharm[1, 2] Dr Pierre Yassa,PhD[3,] Dr Monica Kapasa,MMED[4] Dr Subashi Hira, Dr Mwenya Kwangu,MD[1] Gibson Sijumbila,MD[1*]

[1] Department of Physiological Sciences, School of Medicine, University of Zambia, Zambia
[2] Department of Pharmacy, University Teaching Hospital, Lusaka, Zambia
[3] Department of Internal Medicine, University Teaching Hospital, Lusaka, Zambia.
[4]Department of Paediatrics, University Teaching Hospital, Lusaka, Zambia.

Abstract

Drugs from the group of xanthines (caffeine and aminophylline) are frequently used to manage premature neonates. This study investigates the effects of aminophylline loading dose administration on serum sodium levels in premature neonates admitted Neonatal Intensive Care Unit (NICU) at the University Teaching Hospital (UTH). We evaluated the effects of aminophylline loading dose on serum sodium ions in premature neonates admitted to NICU at (UTH), Lusaka Zambia. A cross sectional study design was used to answer the question. According to our findings, 165 (51%) of the participants had the serum sodium levels below 135mmol/l and 157 (49%) had their serum sodium levels above 135mmol/l.The findings showed the prevalence rates of hyponatremia to be highest in the weight category of 1-1.5kg and the lowest in the weight category of >1.5kg. We found that weight and gestational age has a significant association with serum sodium levels as evidenced by the P=values (0.041 and 0.009) by multivariate linear regression. In our results the majority of the premature neonates showed a significant decrease in serum sodium levels after taking a loading dose of aminophylline. These results suggest that premature neonates on aminophylline could actually benefit from supplements of sodium ions.

Keys words: Level of sodium, Gestational age, Weight, Aminophylline

*Corresponding Author: Dr Gibson Sijumbila, Department of Physiological Sciences, School of Medicine, University of Zambia, Lusaka, Zambia. E-mail: gibson.sijumbila@unza.zm

Received: May 17, 2014 Accepted: July 05, 2014. Published: September 20, 2014.

Introduction

Hyponatremia, which is mainly defined as serum sodium ions less than 135mmol/l, is a very common disorder in premature neonates [1]. It accounts for about 30% of hospitalised cases worldwide, especially in premature neonates admitted to an intensive care unit [2]. In the United States of America, the reported frequency varies from 10-30% among hospitalized paediatric patients. In India, the frequency of hyponatremia is reported to be at 29.8% and the overall morbidity and mortality worldwide stands at 42% [3, 4].

In many cases the cause of hyponatremia is thought to be an exaggerated response to the physiological transition from the intrauterine environment to neonatal independence [5]. On the other hand many studies in adults and neonates have demonstrated a diuretic effect of aminophylline (an adenosine receptor antagonist) due to increased renal blood flow and the inhibition of solute reabsorption in various segments of the nephron as one of the causes of hyponatremia in the neonates [6]. Aminophylline is a soluble inactive ester of theophylline that requires hydrolysis to its active forms of theophylline and ethylenediamine [7]. In the neonatology unit at UTH, aminophylline is used to treat apnea of prematurity in neonates with less than 1.5kg weight, at a loading dose of 5mg/kg followed by a 12 hourly maintenance dose of 2.5mg/kg [8].

Supplements of sodium ions are given as part of routine care to neonates who are on oral feeds. Supplementation of neonates on aminophylline with sodium ions was based on findings of other studies in developed countries which showed that aminophylline in premature neonates in most cases leads to increased excretion of sodium ions.

The importance of sodium is found in the transcendence of cellular processes in which it takes part as the main electrolyte in extracellular fluid and is involved in fluid balance and blood pressure control [9]. Clinical studies have shown that premature neonates with chronic hyponatremia may experience poor growth and developmental retardation [10]. Clinically, serum sodium levels less than 120mmol/l, may be asymptomatic but, often present with seizures and can cause death or permanent neurological deficit [11]. This condition is a common paediatric neurological disease which occurs in 10% of children globally [12]. In NICU at the University Teaching Hospital, seizures account for about 30% of admissions [13].

In the NICU at UTH, no studies have ever been done to establish the extent to which aminophylline affects serum sodium levels in premature neonates and whether there is need to continue supplementing the neonates with sodium ions. This study investigates the effects of aminophylline loading dose administration on serum sodium levels in premature neonates admitted to NICU at UTH.

Methods

This study was conducted in the Neonatal Intensive Care Unit at the University Teaching Hospital, Lusaka, Zambia. UTH is a referral for all the hospitals around the country. NICU admits neonates both preterm and term, delivered at UTH and the surrounding areas of Lusaka Province and other parts of the country. The study population was made up of all the premature neonates admitted to NICU at UTH. A cross sectional study design was used. This study investigated the effects of aminophylline loading dose administration on serum sodium levels in premature neonates admitted NICU at UTH. Included were those premature babies less than 28 days old, those who had not been in hospital more than 24 hours at the time of recruitment and those whose mothers had consented. Excluded were ones who had been in hospital more than 24 hours at time of recruitment, those who were being readmitted, those born with birth asphyxia or renal dysfunction and those whose mothers had not given consent.

Based on the expected 30% prevalence of hyponatremia in neonates admitted to NICU at UTH, we enrolled 322 participants in order to identify the true prevalence with precision of +/-5% and 95% confidence interval. The systematic sampling method was employed, where every 3rd person was selected for the study. Enrolment was done with the help of research assistants who were recruited among the nursing staff in NICU until we reached the sample size of 322. Patients were screened and enrolled between 07:00 hours in the morning and 17:00 hours in the evening of every day of the week during the study period. Blood samples (2mls) were collected from the femoral vein on admission and 12 hrs after the loading dose of aminophylline. And the samples of neonates' blood were collected by the admitting doctor as part of the routine standard care. Blood samples collected were sent to the paediatrics laboratory for the analysis of serum concentration of sodium ions using Pentra C400 Horiba equipment.

Results of laboratory tests of serum sodium levels were entered in the data entry form. The following variables were captured and measured in this study as recorded in Table 1.

Table 1: Variables of the study

Name	Type	Definition	Scale
Level of sodium	Dependent	mmol/l of sodium ions in blood	Continuous
Aminophylline	Independent	mg/kg of aminophylline loading dose	Continuous
Age	Independent	Number of hours after birth	Continuous
Gestational age	Independent	Number of weeks at birth	Continuous
Weight	Independent	Number of grams a neonate weighs on scale	Continuous
Sex	Independent	Male/female	Categorical
Random blood glucose level	Independent	mmols/l of glucose in blood	Continuous

Data was analysed using STATA Version 12 (STATA Corporation, College Station, Texas). Descriptive and statistical analysis was conducted to answer the questions formulated in this study. For

ISSN: 1694-1217 JMST. An open access journal

continuous variables (Sodium levels, Age, Weight of neonate, Gestational age, Aminophylline and IV fluid administration in 12 hours) the mean and standard deviation were calculated. For categorical variables the percentages and histograms were done. To calculate the prevalence rate of hyponatremia in NICU at UTH, a pie chart was used. This study also used a two way bar to establish the change in serum sodium levels after participants were given a loading dose of aminophylline. Population means of serum sodium levels before and after taking aminophylline were compared using t test. A core set of background variables that are believed to be associated with hyponatremia such as age, weight, gestational age were defined. Then the significance of these factors was tested by using a multivariate linear regression.

Results

This section shows the results that indicate the serum sodium changes after loading dose of aminophylline and some factors that may be associated with hyponatremia in NICU at UTH.

Descriptive statistics for the continuous variables (table 2), showed that the mean weight of the participants was 1.44 ± 0.44kg, the mean age was 3.37 ± 3.88hrs, the mean RBS was 3.67±1.81mmols/l and mean gestational age was 31.85 ± 3.01 weeks.

Table 2: Descriptive statistics for continuous variables in the sample (N=322).

Variable	Mean	Std. Dev
Weight (kilograms)	1.44	0.44
Age (Number of hours after birth)	3.37	1.88
Sodium levels before aminophylline administration(mmol/l)	**134.43**	**11.21**
Blood glucose level (mmols/l)	3.67	1.81
Gestation (Number of weeks at birth)	31.85	3.01

As depicted in figure 1, out of the total of 322 we had 197(61%) females while 125(39%) were males.

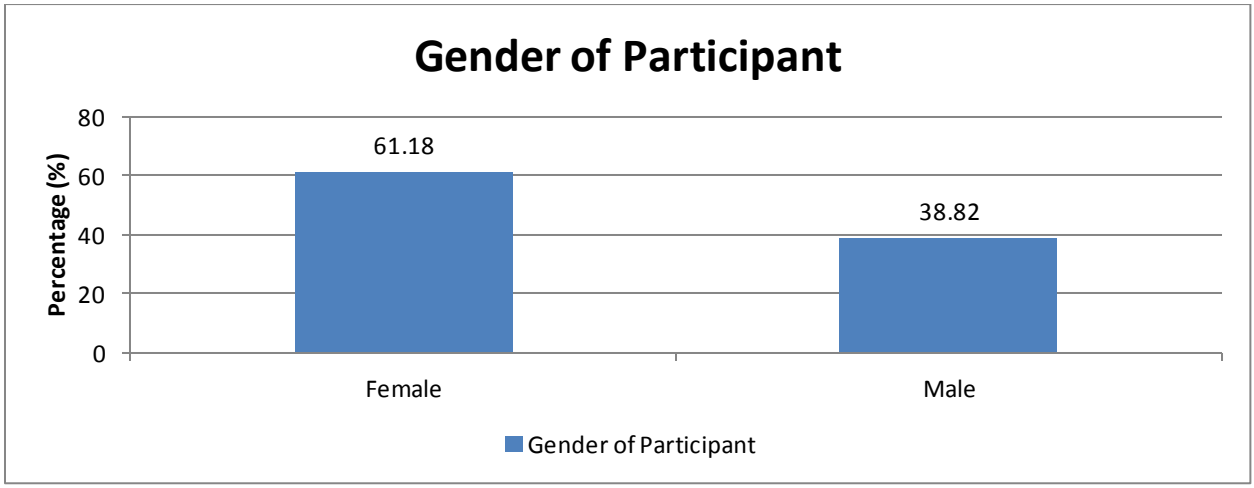

Figure 1: Gender distribution of Participants

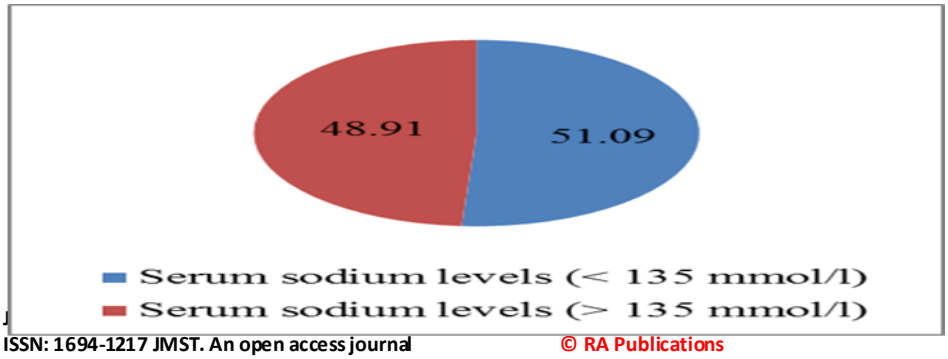

Figure 2: Baseline Prevalence (%) of hyponatremia in premature neonates admitted to NICU at UTH

ISSN: 1694-1217 JMST. An open access journal

Further, our study showed a significant difference in the percentage distribution of serum sodium levels by weight category (table 3). The findings showed the prevalence rates of hyponatremia to be highest in the weight category of 1-1.5kg and the lowest in the weight category of >1.5kg.

Table 3: Percentage Distribution of Serum Sodium levels by weight category of the participants

Weight category (kg)	Serum sodium levels (< 135 mmol/l)	Serum sodium levels (> 135 mmol/l)
	%	
0.4 to 0.9	25	2.55
1 to 1.5	51.22	47.13
>= 1.5	23.78	50.32

The mean serum sodium levels for the participants before and after aminophylline administration was found to be 134.5 ± 11.4 mmol/l and 128.7 ± 9.31mmol/l respectively as shown in table 4.

Table 4: Summary statistics for sodium levels before and after taking aminophylline, (N=188)

Variable	Mean	Standard Deviation
Serum sodium levels before	134.5	11.4
Serum sodium levels after	128.7	9.31

Figure 3 shows the change in the serum sodium levels after taking aminophylline. It is clear that the majority of the participants experienced positive change (reduction in the serum sodium levels) indicated by bars above the zero (0) mark compared to those below.

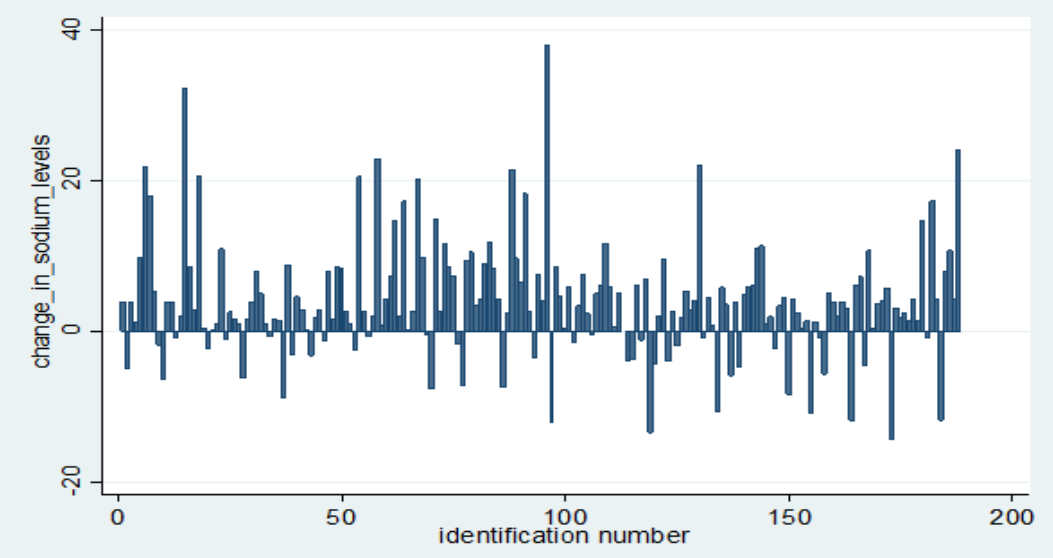

Figure 3: Two way bar showing the change in serum sodium levels after taking aminophylline by the participant ID (N=188).

Table 5 shows the findings after comparing the population means of serum sodium levels before and after taking aminophylline using the t test. The results indicate that the means are statistically different at 5% significance level as the value of t is greater than zero (0).

ISSN: 1694-1217 JMST. An open access journal

Tables 5: Paired two-sample t test with equal variances

Variable	N	Mean	Std. Dev.	95% Confidence Interval	
Serum Sodium before administration of the drug	188	134.5	11.39	130.83	137.11
Serum Sodium after administration of the drug	188	128.67	9.31	127.33	130.00
Diff		3.80	7.66	2.70	7.90
diff = mean(sodium1)-mean(sodium2)				t = 6.8065	
Ho: diff = 0 Ha: diff>0 ; Pr(T > t) =0					

From table 6 below, it can be seen that, weight and gestational age has a significant association with serum sodium levels as evidenced by the P=values (0.041 and 0.009) which are below 5%. From the coefficient of regression it can be seen that, for weight and gestational age the relationship is positive as opposed to age, and RBS that had an inverse relationship to serum sodium levels.

Table 6: Multivariate linear regression results with serum sodium levels before administration of aminophylline as the dependent variable

Independent Variables	Coef.	t	P>t	95% Confidence Interval	
Weight	4.525	1.75	0.041	0.568	9.617
Age	-0.142	-0.89	0.372	-0.455	0.171
Gestation	0.746	2.65	0.009	0.191	1.300
RBS	-0.300	-0.96	0.339	-0.915	0.316
R-squared = 0.210					
N= 321					

Discussion

Our study discusses the effects of aminophylline on serum sodium levels in premature neonates admitted to NICU at UTH in Lusaka Zambia. From the study findings we established that the majority of the premature neonates showed a decrease in serum sodium levels after taking a loading dose of aminophylline. This effect of aminophylline has potential to induce severe hyponatremia in premature babies as they are already prone to hyponatremia [14]. Hyponatremia in preterm infants is an iatrogenic complication that should be preventable, because new-borns start out life with normal serum sodium concentrations [11]. Preterm neonates are at high risk for the development of hyponatremia because of lower glomerular filtration rate, reduced proximal tubular reabsorption of sodium, and increased arginine vasopressin levels in response to illness [10]. In addition regulatory mechanisms of the Na^+ K^+ ATPase are immature in premature babies which means the ability to excrete or retain sodium is limited [6]. Regulation of serum sodium is very important as it determines the size of the extracellular compartment and is also a permissive growth factor. Chronic sodium deficiency is associated with poor

skeletal and tissue growth and adverse neurodevelopmental outcome [12].

Hyponatremia has also been found to be a significant risk factor for development of neurological conditions like deafness, cerebral palsy, intracranial haemorrhage [15] and mortality in those who had asphyxia at birth is high [1].

Our observation on the effect of aminophylline on serum sodium in premature babies is in line with the findings of other authors. Mazkereth et al. 1997 loaded 19 premature infants with a mean gestational age of 31.1 weeks with 6 mg/kg aminophylline followed by maintenance therapy of 2 mg/kg every 12 hours. In this series, a marked diuresis occurred immediately after the loading dose, but most of the effects were not evident after 24 hours despite the continued therapy [16]. Pretzlaff et al. 1999 found that a bolus of 6 mg/kg aminophylline given to eight children aged 1 month to 6 years already receiving a continuous infusion of furosemide increased urine output by over 80% and increased sodium and potassium excretion. All variables returned to baseline by 6 hours [17].

Hocher, 2010 linked the observed effect of aminophylline on the kidneys to the adenosine A1 receptors [6]. Adenosine A_1-receptors located in the afferent arteriole and proximal tubule can contribute to fluid retaining disorders by mediating tubuloglomerular feedback, afferent arteriole vasoconstriction or direct sodium absorption. Aminophylline which is an adenosine A_1-receptor antagonist can increase diuresis and natriuresis and preserve the glomerular filtration rate. Since premature babies are prone to hyponatremia, administration of aminophylline for treatment of apnea can give rise to severe hyponatremia

The findings by Hocher, 2010 can possibly explain the significant reduction in the serum sodium levels that were observed in the premature neonates in our study in NICU at UTH after a loading dose of aminophylline. The findings showed that the changes were significant at 5% significance level. Among the factors that were found to be associated with hyponatremia in NICU at UTH in our study was weight, gestational age which positively associated with serum sodium levels while the age and random blood sugar were inversely associated with serum sodium levels. The positive association of weight and gestational age with serum sodium levels can be due to relative maturity of the salt and water regulatory mechanisms in babies [18]. The renal salt wasting seen in preterm babies below 32weeks of gestation is due both to impaired reabsorption at the proximal tubule, resulting in a higher distal sodium delivery, and to limited aldosterone responsiveness at the distal tubule.

The effect of random blood sugar on serum sodium levels has also been reported by others. Marcialis et al. 2011, in his clinical reviews reported a hypertonic hyponatremia which he attributed to high glucose levels in the blood [10]. There is enough clinical evidence to support these findings as suggested by Mitrovic-Jovanovic et al 2012, where they reported that rearbsorption of water drawn by molecules like glucose (hyperglycemia or diabetes) lead to hyponatremia, thereby glucose being inversely related to serum sodium levels [4]

Conclusion

The study established that the majority of the premature neonates showed a decrease in serum sodium levels after taking a loading dose of aminophylline. This study therefore suggests that there is a difference in the serum sodium levels before and after aminophylline loading dose in premature neonates admitted to NICU at UTH and those premature neonates on aminophylline could actually benefit from supplements of sodium ions.

Weight and gestational age were significantly associated with hyponatremia. Further research on supplement of sodium ions to premature neonates needs to be conducted.

Acknowledgements

We would like to thank the mothers for allowing us to get valuable data from their babies. We would also like to thank all the members of staff in the Paediatric Neonatal Intensive Care Unit for the help they rendered during the recruitment process of participants. Our thanks also go to the Paediatric Laboratory for helping us in sample analysis. The study was partly funded by the Medical Education partnership Initiative.

References

1. Suhardjono, Hyponatremia, prevalence, diagnosis, and management. Acta Med Indones, 2011. 43(3): p. 149-51.

2. Daftary, A.S., S.K. Patole, and J. Whitehall, Hypertension-hyponatremia syndrome in neonates: case report and review of literature. Am J Perinatol, 1999. 16(8): p. 385-9.
3. Marcialis, M.A., et al., Hyponatremia and hypernatremia in the newborn: in medio stat virtus. Front Biosci (Elite Ed), 2012. 4: p. 132-40.
4. Mitrovic-Jovanovic, A., et al., Comparison of electrolytic status (Na+, K+, Ca2+, Mg2+) in preterm and term deliveries. Clin Exp Obstet Gynecol, 2012. 39(4): p. 479-82.
5. King, R.I., et al., Electrolytes in sick neonates - which sodium is the right answer? Arch Dis Child Fetal Neonatal Ed, 2013. 98(1): p. F74-6.
6. Hocher, B., Adenosine A1 receptor antagonists in clinical research and development. Kidney International, 2010. 78(5): p. 438-445.
7. Migliori, C., et al., Aminophylline treatment of refractory bronchospasm in mechanically ventilated neonates: case report. Med Sci Monit, 2007. 13(8): p. CS93-6.
8. NICU treatment protocol 2010 Neonatal Intensive Care Unit University Teaching hospital Lusaka Zambia 2010 version.
9. Coimbra, T.M., et al., Renal Development and Blood Pressure in Offspring from Dams Submitted to High-Sodium Intake during Pregnancy and Lactation. Int J Nephrol, 2012. 2012: p. 919128.
10. Marcialis, M.A., et al., Neonatal hyponatremia: differential diagnosis and treatment. J Matern Fetal Neonatal Med, 2011. 24 Suppl 1: p. 75-9.
11. Baraton, L., et al., Impact of changes in serum sodium levels on 2-year neurologic outcomes for very preterm neonates. Pediatrics, 2009. 124(4): p. e655-61.
12. Karbasi, S.A., M.M. Mosadegh, and R. Fallah, Utility of laboratory studies in seizures of children older than one month of age. Singapore Med J, 2009. 50(8): p. 814-6.
13. NICU ward statistics 2012 Neonatal Intensive Care Unit University Teaching hospital Lusaka Zambia 2012 report.
14. Assadi, F., Hyponatremia: a problem-solving approach to clinical cases. Journal of Nephrology, 2012. 25(4): p. 473-480.
15. Li, Y.F., G.J. Lu, and Y.K. Han, [Risk factors for intracranial hemorrhage in very low birth weight infants]. Zhongguo Dang Dai Er Ke Za Zhi, 2007. 9(4): p. 297-300.
16. Mazkereth, R., et al., Effects of theophylline on renal function in premature infants. Am J Perinatol, 1997. 14(1): p. 45-9.
17. Pretzlaff, R.K., R.J. Vardis, and M.M. Pollack, Aminophylline in the treatment of fluid overload. Crit Care Med, 1999. 27(12): p. 2782-5.
18. Field, M.J., Comment on "Does 'asymptomatic hyponatremia' exist?". Nat Rev Nephrol, 2010. 6(6): p. 1.

