THE UNIVERSITY OF ZAMBIA
SCHOOL OF MEDICINE
DEPARTMENT OF PHYSIOLOGICAL SCIENCES

The prevalence of hyponatremia and effects of aminophylline on serum sodium ions in premature neonates admitted to Neonatal Intensive Care Unit, at the University Teaching Hospital, Lusaka, Zambia.

A Dissertation submitted
By
MUKOSHA MOSES

In partial fulfillment of the requirement for the award of the degree of Masters of Science in Biochemistry

SUPERVISOR: DR GIBSON SIJUMBILA
CO-SUPERVISORS: DR PIRRE YASSA AND DR MONICA KAPASA

CERTIFICATE OF APPROVAL

The University of Zambia approves this dissertation of **Mukosha Moses** in partial fulfilment for the requirements for the award of the degree in Master of Science in Biochemistry.

Examiner's signature Date

....

Examiner I

....

Examiner II

....

Examiner III

Head of Department

Signature..... Date.....

CERTIFICATE OF COMPLETION OF DISSERTATION

I, **Mukosha Moses,** do hereby certify that this dissertation is the product of my own work and in submitting it for my Master of Science in Biochemistry programme, further attest that it has not been submitted to another University in part or whole for the award of any programme.
Signature..... Date.....

I, **Dr G.Sijumbila**, having supervised and read this dissertation is satisfied that this is the original work of the author under whose name it is being presented. I confirm that the work has been completed satisfactorily and is ready for presentation to the examiners.

Supervisor: **Dr G.Sijumbila**
Supervisor's signature.....
Date.....

Head of Department
Signature..... Date.....
Department of Physiological Sciences, School of Medicine, University of Zambia

DECLARATION

I hereby declare that this dissertation represents my own work and has not been presented either wholly or in part for a degree at the University of Zambia or any other university.

Signed: _____ Date_____

Student: Mukosha Moses (Msc Pharm)

I have read this dissertation and approved it for examination

Signed: _____Date_____

Supervisor: Dr. G. Sijumbila MD

ABSTRACT

BACKGROUND: Hyponatremia, defined as serum sodium less than 135mmol/l, is a very common disorder in neonates. It accounts for about 30% of hospitalised cases worldwide, especially in premature neonates admitted to an intensive care unit. The overall morbidity and mortality from hyponatremia worldwide is reported to be at 42%. Studies done in adults and neonates have demonstrated that aminophylline, an adenosine A1 receptor antagonist, has a diuretic effect and has been implicated in lowering serum sodium levels in premature neonates. However these studies did not address the need for sodium supplementation for neonates receiving aminophylline. This study aimed at determining the prevalence of hyponatremia in premature neonates, and the effects of aminophylline administration on serum sodium levels in Neonatal Intensive Care Unit (NICU) at the University Teaching Hospital (UTH).

METHOD: A cross sectional study design was employed to study 322 premature neonates who were enrolled between October 2013 and February 2014. The mean weight and mean gestational age of the participants was 1.44kg and 31.85 weeks respectively. Out of the 322 participants 188 met the criteria for aminophylline administration and were given a loading dose. As part of routine management, blood samples were collected on admission and 12hours after a loading dose of aminophylline. The blood samples were taken to UTH paediatrics laboratory for analysis. The analysis involved measuring the serum sodium levels using Pentra C400.

RESULTS: According to the findings, this study shows that in premature neonates the prevalence of hyponatremia in NICU at UTH is 51%. The study further established that the majority of the premature neonates showed a significant decrease in serum sodium levels after taking a loading dose of aminophylline with *P*-value 0.0000. Among the factors that the study looked at, weight and gestational age, were significantly associated with hyponatremia with *P*-values 0.041 and 0.009 respectively.

CONCLUSION: The prevalence of hyponatremia in NICU at UTH is significantly high and using aminophylline in premature neonates lowers serum sodium levels and sodium supplements may be required. Among the factors that the study looked at, only weight and gestational age

were significantly associated with hyponatremia in premature neonates admitted to NICU at UTH.

Nevertheless, the renal actions of aminophylline in premature neonates merit further investigation.

DEDICATIONS

This dissertation is dedicated to my wife Dr Nyundo Wachi, and my children, Vivian and Maureen, for their understanding, love and support when I was away from them for long hours during my studies.

ACKNOWLEDGEMENTS

I wish to thank my supervisors Dr Gibson Sijumbila, Dr Piere Yassa and Dr Monica Kapasa for their patience and guidance during the development of the proposal and the write up of my dissertation.

I would like to thank the Neonatal Intensive Care Unit (NICU) team, the graduates' forum for the contribution and guidance through the proposal development and actual implementation of the study. Thanks to Dr Ben Andrews for the guidance on proposal development.

My thanks go to the mothers and their babies who participated in this research, without whom, this work may not have been made possible.

Special thanks go to my classmates with whom I shared a lot of good moments, and my young man Dr Mwenya Kwangu, for always reminding me of deadlines to complete this wonderful piece of work

TABLE OF CONTENTS

LIST OF FIGURES

LIST OF TABLES

LIST OF ABBREVIATIONS

[Na]	-	Serum Sodium Concentration
AVP	-	Arginine Vasopressin Hormone
CNS	-	Central Nervous System
ECF	-	Extracellular Fluid
EGA	-	Expected Gestational Age
NICU	-	Neonatal Intensive Care Unit
PTH	-	Parathyroid Hormone
SIADH	-	Syndrome of Inappropriate Antidiuretic Hormone Secretion
UNZABREC	-	University of Zambia Biomedical Research Ethics Committee
UTH	-	University Teaching Hospital
WHO	-	World Health Organisation
RVD	-	Retroviral disease
RBS	-	Random Blood Sugar

DEFINITION OF TERMS

Aminophylline - A drug used in NICU at UTH for treatment of apnoea of prematurity. It is a methyl xanthine derivative which is made up of the mixture of theophylline and ethylene-diamine in a ratio of 2:1.

Apnoea - Absence of breath for about 20 – 30 Seconds

Apnoea of prematurity - Apnoea occurring in premature neonates, due to prematurity

Hyponatremia - Serum concentration of sodium ions less than 135 mmol/l

Neonate - A new born infant below 28days of life

Premature neonate - Neonate below 37 completed weeks of gestation age

Term neonate - Baby born between 37 completed weeks and 40 weeks of gestation

1.0 BACKGROUND

Hyponatremia, which is mainly defined as serum sodium less than 135mmol/l, is a very common disorder in neonates (Karbasi et al., 2009, Assadi, 2012, Suhardjono, 2011). It accounts for about 30% of hospitalised cases worldwide, especially in premature neonates admitted to an intensive care unit (Daftary et al., 1999). According to the World Health Organisation (WHO), In the United States, the reported frequency varies from 10-30% among hospitalized pediatric patients with premature neonates accounting for more than half of the cases. In India, the frequency of hyponatremia is reported to be at 29.8% and the overall morbidity and mortality worldwide stands at 42% (Marcialis et al., 2012, Mitrovic-Jovanovic et al., 2012).

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 (Coimbra et al., 2012). Clinical studies have shown that premature neonates with chronic hyponatremia may experience poor growth and developmental retardation (Marcialis et al., 2011). Clinically, serum sodium levels less than 120mmol/l, in premature neonates may be asymptomatic because of relative immature nervous system but, often present with seizures and can cause death or permanent neurological deficit (Thomas et al., 2012). This condition is a common paediatric neurological disease which occurs in 10% of children globally (Karbasi et al., 2009). In Neonatal Intensive Care Unit (NICU) at the University Teaching Hospital (UTH), seizures account for about 30% of admissions due to different causes (NICU ward statistics., 2012).

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 (Hsu and Levine, 2004). On the other hand many studies in adults and neonates have demonstrated a diuretic effect of aminophylline (an adenosine A1 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 (Pretzlaff et al., 1999, Lowry et al., 2001). Aminophylline is a soluble inactive ester of theophylline that requires hydrolysis to its active forms of theophylline and ethylene-diamine (Ahn et al., 1999).

In the neonatology unit at UTH, aminophylline is used to treat apnoea of prematurity in premature neonates less than 1.5kg of weight at a loading dose of 5mg/kg followed by a 12

hourly maintenance dose of 2.5mg/kg (NICU treatment protocol., 2010). Supplements of sodium ions are given as part of routine care to neonates who are on oral feeds. Any new-born that develops apnoeic spells is worked up for possible causes of apnoea such as obstructive apnoea, anaemia, sepsis, hypoglycaemia and electrolyte imbalance. If these causes are ruled out and the baby is premature, regardless of gestation age, this is presumed to be apnoea of prematurity and the baby is given aminophylline therapy with supplements of sodium. 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 (Ahn et al., 1999, Ng et al., 2005, Pretzlaff et al., 1999, Lowry et al., 2001).

In NICU at UTH, the prevalence rate of hyponatremia is estimated at 30% (NICU ward statistics., 2013). However, from the ward statistics, the prevalence has been on the rise in the recent past, a situation that calls for quick interventions. The rise in estimated prevalence could be attributed to the increase in orders for baseline electrolytes from the paediatricians than before.

From the above discussion, it can be seen that aminophylline can have an effect on serum sodium levels which may culminate into hyponatremia.
This study investigated the prevalence of hyponatremia in premature neonates, and the effects of aminophylline administration on serum sodium levels in NICU at UTH.

1.1 STATEMENT OF THE PROBLEM

Hyponatremia is the major cause of paediatric neurological disease and developmental retardation (Thomas et al., 2012). One of the factors that contribute to hyponatremia is the use of aminophylline which has an effect on serum sodium levels (Ahn et al., 1999).
In the case of NICU at UTH, studies have not been done in this unit 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.
The prevalence rates of hyponatremia in premature neonates worldwide stands at 29% (Assadi, 2012). There are no known reported studies on prevalence of hyponatremia and effects of aminophylline on serum sodium ions in neonates in the sub-region and in Zambia at the time of this study. Hence, we needed to study hyponatremia due to the high estimated

prevalence rates of 30% in NICU at UTH, and the significant role this deficiency may play in the paediatric neurological disease and developmental retardation

1.2 STUDY JUSTIFICATION

In the previous studies which showed increased loss of sodium ion in neonates who were put on aminophylline, studies did not address the need for sodium supplementation (Pretzlaff et al., 1999, Modlinger and Welch, 2003). This study aimed to address this gap.

The results of this study may act as baseline for more studies regarding hyponatremia and use of aminophylline in premature neonates in NICU. The information from this study may also be useful for policy makers regarding the management of hyponatremia in premature neonates in NICU. The same information generated from this study, may be useful to other researchers in other areas of paediatrics particularly in conditions with electrolyte abnormalities. This study will also benefit the neonates admitted to NICU in that for the subsequent ones the unit will know the approximate amount of sodium ions to supplement.

1.3 RESEARCH QUESTION

What is the prevalence of hyponatremia in NICU at UTH in premature neonates during the period of this study?

1.4 GENERAL OBJECTIVE

To establish the serum sodium levels and effects of aminophylline on serum sodium levels in premature neonates admitted to NICU at UTH

1.5 SPECIFIC OBJECTIVES

I. To determine the baseline prevalence of hyponatremia in premature neonates admitted to NICU at UTH
II. To determine the change in serum sodium levels 12hrs after aminophylline administration.
III. To determine some factors that may be associated with hyponatremia in premature neonates admitted to NICU at UTH

2.0 LITERATURE REVIEW

In the literature hyponatremia is mainly defined as serum sodium levels less than 135mmol/l (Karbasi et al., 2009, Mitrovic-Jovanovic et al., 2012). Assadi, in one of his clinical reviews defined hyponatremia as serum sodium levels less than 135mmol/l, and reported that one of the main causes was elevated levels of arginine vasopressin (AVP) hormone (Assadi, 2012). In this study we defined hyponatremia as any serum sodium levels less than 135mmol/l based on the current UTH paediatrics laboratory reference values (135mmol-145mmol).

Hyponatremia is known to be the most common electrolyte disorder that affects about 20%-30% of patients worldwide, the highest prevalence is reported in India and United States of America. The overall mortality and morbidity stands at 42% (Marcialis et al., 2011, Upadhyay et al., 2006).

In premature neonates, hyponatremia may be due to impaired reabsorption in the proximal tubule, resulting in a higher distal sodium delivery and to limited aldosterone responsiveness in the distal tubule (Suhardjono, 2011, Baajafer et al., 1999). The use of aminophylline in neonates has also been implicated to be among the causes of hyponatremia in this age group (Mazkereth et al., 1997, Pretzlaff et al., 1999).

Aminophylline is a soluble inactive ester of theophylline that requires hydrolysis to its active forms of theophylline and ethylene-diamine. Aminophylline acts as an adenosine A_1 receptor antagonist (Noguchi et al., 1990). 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 (Hocher, 2010). Aminophylline can increase diuresis and natriuresis and preserve the glomerular filtration rate by blocking adenosine A_1-receptor (Modlinger and Welch, 2003).

Variations in free and bound theophylline levels and rate of theophylline metabolism could all contribute to the variation in response to aminophylline infusion among infants. Theophylline is 60% bound to plasma proteins in the blood in adults, but only 40% bound in newborn infants. Theophylline is largely metabolized in the liver prior to urinary excretion.

In premature infants alone it is extensively converted to caffeine, another xanthine, which also blocks adenosine receptors. The rate of elimination of both caffeine and theophylline is greatly reduced in premature infants; the plasma half-life is more than 50 hours for caffeine and 24.7–36.5hours for theophylline (Lowry et al., 2001). Caffeine accumulates in the plasma of premature infants given theophylline to concentrations about 25% of the theophylline levels.

Acute hyponatremia may manifest itself in premature neonates who are born following a course of prenatal steroids (Marcialis et al., 2011). Clinical manifestations vary from an asymptomatic state to severe neurologic dysfunction (Field, 2010). CNS symptoms predominate in hyponatremia, although cardiovascular and musculoskeletal findings may be present (Mitrovic-Jovanovic et al., 2012). Hyponatremia exerts most of its clinical effects on the brain. Severe hyponatremia can cause an osmotic shift of water from plasma into the brain cells which cause clinical manifestations such as confusion, diminished reflexes, convulsions, stupor, or coma (Suhardjono, 2011, Al Qahtani et al., 2013). Assadi, 2012 in a clinical review reported that patients with acute hyponatremia are subject to more severe degrees of cerebral edema for a given serum sodium level. It was concluded that the primary cause of morbidity and death is brainstem herniation and mechanical compression of vital midbrain structures (Assadi, 2012).

The findings in the study by Assadi, may partly explain what is being observed in most of the neonates who present to NICU at UTH with seizures. In many cases the diagnosis of hyponatremia is usually missed and only done as a diagnosis of exclusion i.e after all other common causes of seizures in this unit are ruled out. In this study it is hoped that the results will influence the way hyponatremia is treated.

Marcialis et al. 2011 in their clinical review on how to differentiate hypovolemic, euvolemic and hypervolemic hyponatremia, concluded that, hyponatremia is a complex clinical problem that occur frequently in full term new-borns and in preterm infants admitted to NICU although its real frequency and aetiology is incompletely known. They further reported that, in the neonates, there are still some uncertainties with regards to “how” and “when” hyponatremia alters the neuronal osmotic equilibrium (Marcialis et al., 2011).

Treatment of hyponatremia depends on the cause. Hyponatremia in the ill neonate requires careful assessment. Examination of the intravenous fluid charts, urine output records and the

neonate's weight trend should help. The neonate with total body sodium depletion needs more sodium whereas one who is retaining fluid does not need more sodium, merely fluid restriction (Rennie and Roberton, 2002). Hyponatremia resulting from Syndrome of Inappropriate Antidiuretic Hormone Secretion (SIADH) usually caused by brain (hypothalamic) injury is treated by fluid restriction and treating the primary Central Nervous System (CNS) disorder (Mitrovic-Jovanovic et al., 2012)

This study focused on the aspect of aminophylline use in premature neonates as it is one of the problems currently being experienced in NICU at UTH. Looking at the studies that have been done which have implicated aminophylline in depleting serum sodium levels (Ng et al., 2005, Marcialis et al., 2011, Mazkereth et al., 1997), and also the fact that aminophylline is being used in NICU, this study expanded on and filled the gap (need to supplement the neonates being treated with aminophylline) in the literature.

Studies that have been done on electrolytes in neonates have shown varying degrees of hyponatremia, but they all concluded or showed the importance of determining electrolytes (Na+) in this group (Hohenschild and Paust, 1993, Thomas et al., 2012, Marcialis et al., 2012, Daftary et al., 1999).

Furthermore, these studies focused on effects of aminophylline on the developing kidney and relationship between gestational age and hyponatremia and have not addressed the need to supplement neonates who are put on this drug (Mazkereth et al., 1997, Zanardo et al., 1990, Pretzlaff et al., 1999)

In a study to evaluate the effects of aminophylline on the developing kidney, a loading infusion of 6mg/kg aminophylline, followed by maintenance therapy at 2mg/kg every 12 hours was given. The results showed a marked diuresis immediately after loading dose. However, it was reported that most of the effects were no longer evident after 24 hours, despite continuing aminophylline maintenance therapy. It was concluded that in premature infants the aminophylline loading dose, but not the maintenance therapy, affected renal functions (Mazkereth et al., 1997).

Pretzlaff et al. 1999 found that a bolus of 6 mg/kg aminophylline given to eight children aged between 1 month and 72months 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 (Pretzlaff et al., 1999).

These studies suggest that aminophylline affect the serum sodium levels and could be the case with the neonates in NICU at UTH who are currently being treated with this drug. Nevertheless, more research is still needed to establish the need to supplement the neonates put on aminophylline. In this present study the aspect of sodium supplementation was addressed.

In a study to determine the, clinical and biochemical effects of dietary sodium supplements of 4 to 5mmol/kg/day on neonates, 22 infants of gestational age 27 to 34weeks from days 4 to 14 of life were studied. These infants were compared with a group of 24 unsupplemented infants. The infants who were supplemented lost less weight postnatally and regained birth weight more quickly. Their improved weight gain continued even after supplementation was stopped. Sodium balance was positive at age 5 to 11days in supplemented infants but slightly negative in controls. It was concluded that the infants who were supplemented showed improved weight and had less complications associated with low birth weight and prematurity (Al-Dahhan et al., 1984).

In NICU at UTH, the gestational age is not considered as the protocol only specifies for neonates who are less than 1.5kg for eligibility. Neonates born under 34 weeks at a birth weight above 1.5kg are not considered for aminophylline and subsequent sodium supplementation. In this study, information on gestation age was collected and the best parameter to use with age was established. Furthermore, the study by Al-Dahhan et al, 1984, was slightly different from this one in that in this study, the participants' ages were less than 24hrs.

In Africa there are very few studies that have been done in relation to neonatal hyponatremia, its prevalence and associated risk factors.

In a study done in Nigeria, serum electrolytes of 80 clinically stable new-borns comprising 60 preterm and 20 term appropriate for gestational age babies were prospectively studied and the results showed a negative correlation between the serum sodium and the gestational age (Adedoyin et al., 2001).

In this study the focus was on premature neonates only and it was expected to be comparative to the study conducted in Nigeria, However this study went further to establish the extent to which aminophylline affects serum sodium levels in this group apart from the factor of prematurity.

In Zambia currently there is paucity of data regarding the prevalence of hyponatremia in neonatal intensive care unit and serum concentration of sodium in neonates receiving aminophylline.

Despite the substantial advances made, many questions still remain without solutions as concerns hyponatremia and its treatment in neonates (Marcialis et al., 2011, Moritz and Ayus, 2009).

In conclusion to this literature review, it is clear that many questions have not yet been addressed and further research is needed to address the current health needs in NICU at UTH, in particular the need to supplement the neonates on aminophylline and establish the effects of aminophylline administration on serum sodium levels in premature neonates admitted to NICU at UTH. This study focused on these gaps and sort to provide answers that will help in the management of neonates in NICU at UTH.

3.0 RESEARCH METHODS

This section provides the details of the research strategy that was adopted to address the research issues that were identified in the objectives, together with the means of collecting data for analysis, including ethical issues that were considered.

3.1 STUDY DESIGN

A cross sectional study design was used. A cross-sectional study can either be descriptive or analytical. Prevalence studies normally utilise descriptive cross-sectional study, and studies involving a comparison of prevalence among exposed and non-exposed use analytic cross-sectional study (Patarawan, 2005). Since, this study was evaluating hyponatremia before and after aminophylline administration among premature neonates a cross-sectional study design was suitable for this study.

3.2 STUDY SITE

This study was conducted at the Neonatal Intensive Care Unit at the University Teaching Hospital, Lusaka, Zambia. NICU admits neonates both preterm and term, delivered at UTH and the surrounding areas of Lusaka Province and other parts of the country. Neonates are admitted and treated following the currently revised NICU protocol 2010. During the period of the study, concentration of serum sodium ions was measured routinely on premature neonates on admission as standard of care.

3.3 TARGET POPULATION

All premature neonates admitted to NICU

3.4 STUDY POPULATION

The study population was the premature neonates admitted to the NICU at UTH who met the inclusion criteria.

3.5 INCLUSION CRITERIA

- Premature neonates admitted to neonatal intensive care unit at UTH for the first time
- Preterm neonates below 37 completed weeks of gestation.
- Admitted to NICU less than 24hours before screening/enrolment
- Neonates whose mothers have given a consent

3.6 EXCLUSION CRITERIA

- Neonates who were being re-admitted to neonatal intensive care unit at UTH
- Neonates more than 24hours of admission
- Neonates with birth asphyxia
- Neonates with renal failure
- Neonates whose mothers have not given a consent

3.7 SAMPLE SIZE

Based on the expected 30% prevalence of hyponatremia in neonates admitted to neonatal intensive care unit (NICU) at UTH, we needed to enroll 322 participants in order to identify the true prevalence with precision of +/-5% and 95% confidence interval.

$$N = \frac{Z^2 \times P(1-P)}{d^2} = \frac{1.96^2 \times 0.3(1 - 0.3)}{(0.05)^2} = 322$$

Where **N**-sample size, **Z**-Zstatistic=1.96, **P**- the expected prevalence=30%=0.3, **d**-acceptable accuracy range (+/- 0.05)

3.8 SAMPLING TECHNIQUES

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 (refer to formula above).

3.9 SCREENING AND ENROLMENT

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.

Informed consent was obtained from the mother/caregiver of the neonate using a consent form (appendix I), after it has been read and explained to the mother/caregiver

3.10 DATA COLLECTION

A total of 322 premature neonates aged 0-24hours who met the inclusion criteria were included in the study. Information on the mother and neonates was collected using questionnaire and laboratory form (Appendix III and IV). Blood samples (2mls) were collected from the neonates meeting the criteria on admission and 12hours after the loading dose of aminophylline.

Samples of neonate's blood were collected by the admitting Doctor as part of standard of care. Blood samples collected were sent to the pediatrics laboratory for the analysis of serum concentration of sodium ions using Pentra C400 Horiba equipment.

This was done in the UTH paediatrics laboratory by the laboratory technicians as part of routine standard of care and normal procedures prescribed by the staff from this laboratory of measuring serum sodium ions was followed. Results of laboratory tests of serum sodium levels were entered in the data entry form.

3.11. PRINCIPLES OF PENTRA C400 HORIBA EQUIPMENT

Analysis Method Types:

- Spectrophotometry: Colorimetry and Turbidimetry,
- Potentiometry: Direct (Serum or Plasma) and Indirect (Urine).

For measuring sodium ions in serum using Pentra C400 Horiba equipment in this study the analytical method direct potentiometry was used.

A potentiometer is an instrument for measuring the potential (voltage) in a circuit. Potentiometric determination of sodium remains attractive to analysts because determinations can be made directly on the sample without pre-treatment, the sample remaining essentially unaltered after analysis. Furthermore, electrodes respond to the activity of the ions to which they are sensitive, and this active concentration is often of greater biological significance than the total concentration of biological fluids

The table below shows the variables of interest in our study and how we defined them.

Table 3.1: study variables

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
Ritroviral disease	Independent	Exposed /not exposed	Categorical

(RVD) status			
Sex	Independent	Male/female	Categorical
Random blood glucose level (RBS)	Independent	mmols/l of glucose in blood	Continuous

3.12 DATA ANALYSIS

Data analysis was done using Stata version 12. This section describes the analytical tools that were adopted for this study.

Descriptive: For continuous variables (Sodium levels, Age, Weight of neonate, Gestational age,) the mean and standard deviation was calculated. For categorical (Sex, RVD status,) variables the percentages and histogram was done.

Analytical*:* 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. The comparing of population means of serum sodium levels before and after taking aminophylline was done using a students paired t test and a P value obtained. A P value of less or equal to 5% was considered significant.

To determine some factors that may be associated with hyponatremia, multivariate linear regression was done.

3.13 ETHICAL CONSIDERATION

Before commencement of this study ethical approval was sought from ERES Converge IRB.

After being admitted to NICU the neonates were assessed by the admitting Doctor and if they met the inclusion criteria and the mother consented then they were enrolled. As part of routine management, 2mls of blood was collected from the cubital fossa of the upper right arm and put in the heparin/lithium bottle and sent to the biochemistry laboratory for analysis.

Confidentiality and privacy were maintained during and after data collection. Information on antenatal period and the delivery as well as on the baby was collected and codes for names of mother and neonates were used.

Consent was obtained from the neonate's parents/caregiver using a specially designed consent form (appendix II). The study procedure and objectives were also communicated to the neonate's parent/caregiver in the language they best understood. The parent/caregiver to the neonate did not incur any additional costs as a result of this study.

Findings of the serum sodium levels and the possible immediate and long term implications appropriate for the findings were communicated to the parent/caregiver as soon as they were available. The results were recorded on the neonate's file and promptly made available to the attending Doctors for appropriate management in the immediate period.

4.0 RESULTS

We will present the results based on the objectives that this study was set to achieve. This section shows the results that indicate the prevalence of hyponatremia in NICU at UTH, the serum sodium changes after aminophylline administration and some factors that may be associated with hyponatremia in NICU at UTH.

Descriptive statistics for the continuous variables (figure 4.1), showed that the mean weight of the participants was 1.44 ± 0.44kg. The mean age was 3.37 ± 3.88hrs, the mean Random Blood Glucose (RBS) was 3.67±1.81mmols/l and mean gestational age was 31.85 ± 3.01 weeks

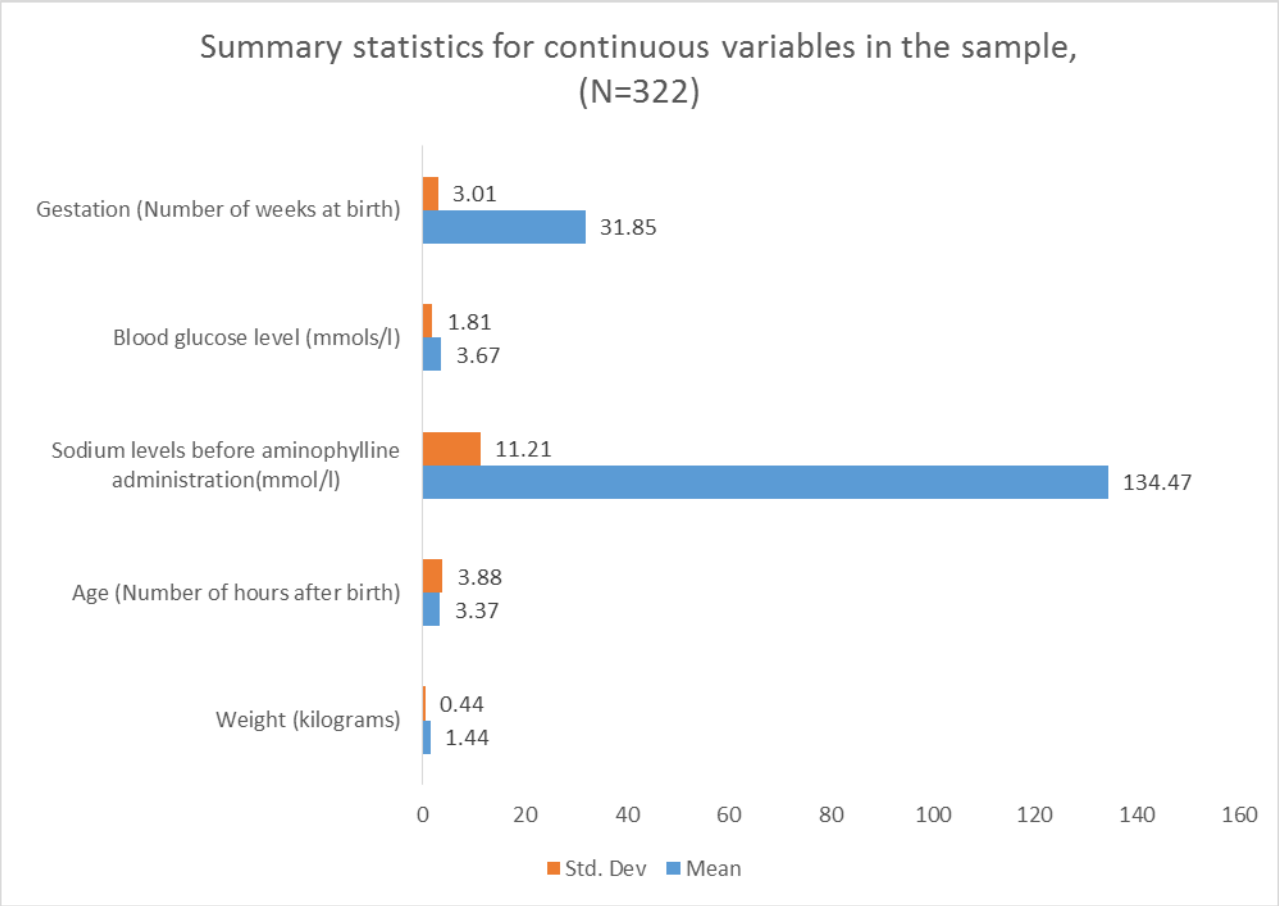

Figure 4.1: Descriptive statistics for continuous variables in the sample, (N=322)

As depicted in figure 4.2, out of the total of 322 there were 197(61%) females and 125(39%) males.

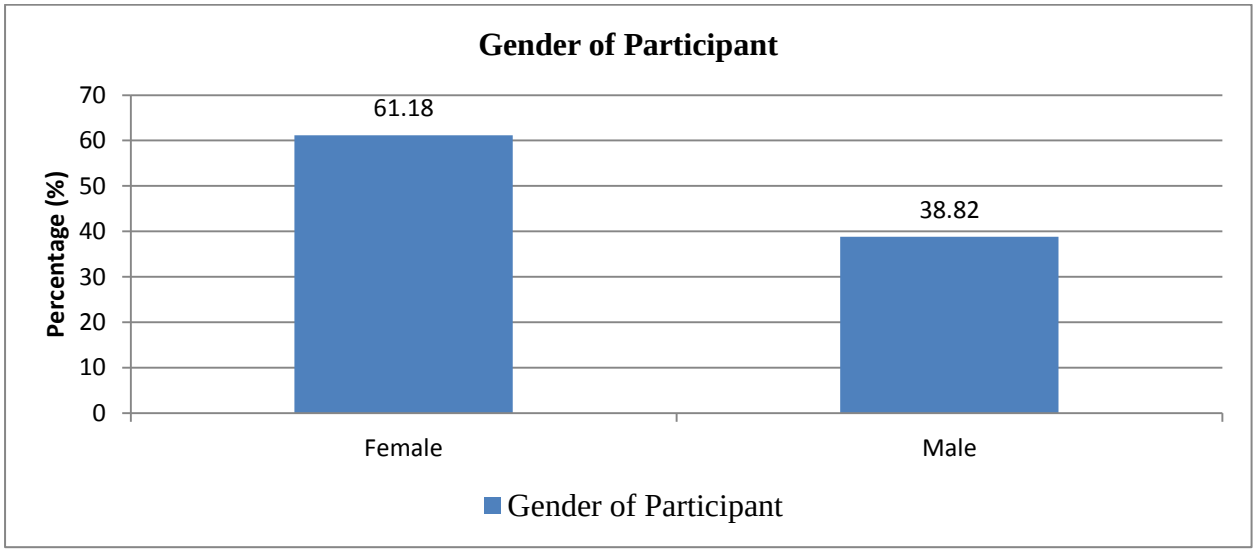

Figure 4.2: Gender distribution of Participants

From the study findings (figure 4.3), 120 (37.27%) of the participants were RVD positive while 202 (62.73%) were RVD negative

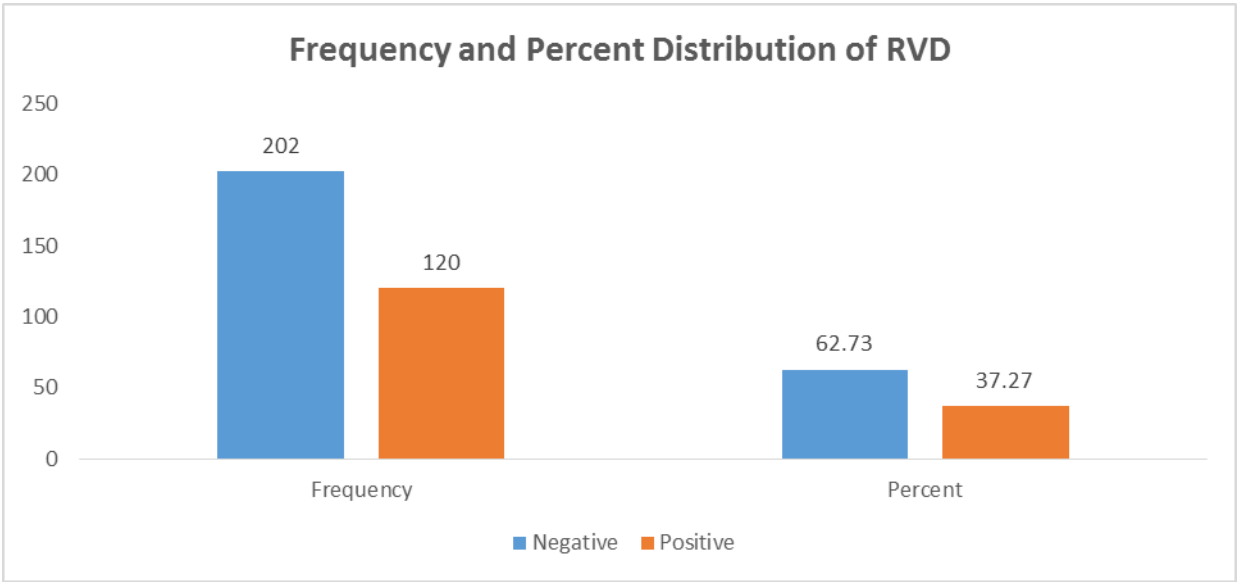

Figure 4.3: the frequency and percentage distribution of participants based on retroviral status (RVD)

4.1 BASELINE PREVALENCE OF HYPONATREMIA IN PREMATURE NEONATES IN NICU AT UTH

This study defined hyponatremia to be any serum sodium levels less than 135mmol/l based on the reference range from the UTH pediatrics laboratory (135mmol/l – 145mmol/l). 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 (figure 4.4).

,

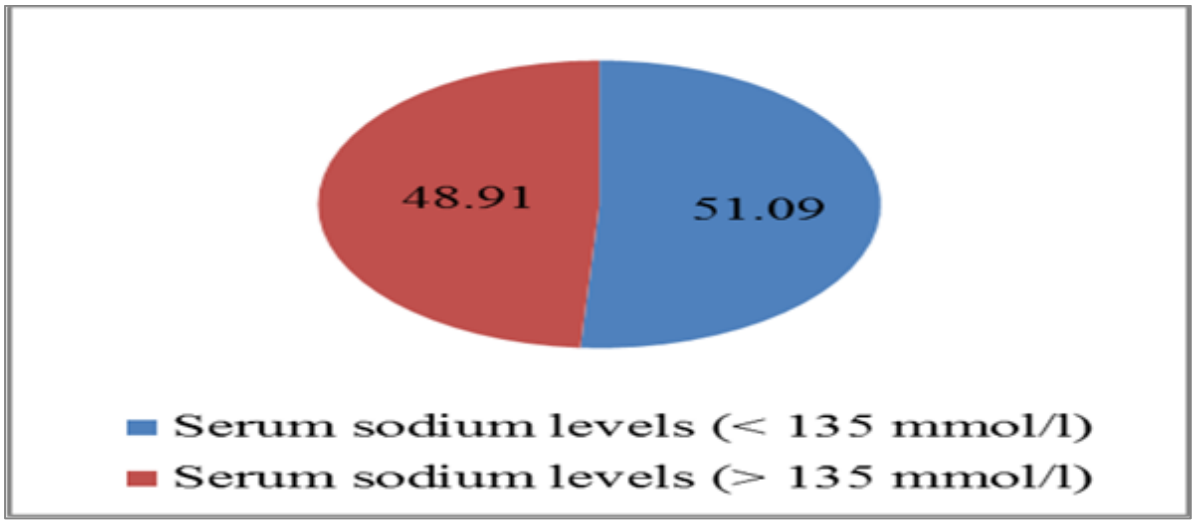

Figure 4.4: Baseline Prevalence (%) of hyponatremia in premature Neonates admitted to NICU at UTH

Further, the results in table 4.1 shows the difference in the percentage distribution of serum sodium levels by weight category. The prevalence rate is highest in the weight category of 1-1.5kg and the lowest in the weight category of more than 1.5kg.

Table 4.1: Percentage Distribution of Serum Sodium levels by weight category of the participants before administration of aminophylline

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 before aminophylline administration were lowest in the weight category (0.4 – 0.9 kg) and highest in the weight category 1.5kg and above and only the weight category greater than 1.5kg showed a large decrease in the mean levels after aminophylline administration (table 4.2)

Table 4.2: The mean distribution of Serum Sodium levels by weight category of the participants before and after aminophylline administration

	Before		**After**	
Weight category and Serum sodium levels	Mean	Std.Dev	Mean	Std.Dev
0.4 to 0.9				
Serum sodium levels (mmol/l)	123.04	11.44	119.47	10.05
1 to 1.5				
Serum sodium levels (mmol/l)	134.54	9.34	131.32	7.04
>= 1.5				
Serum sodium levels (mmol/l)	138.32	10.69	132.86	8.64

4.2 SERUM SODIUM LEVELS 12HRS AFTER AMINOPHYLLINE ADMINISTRATION

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 with the *p*-value of 0.0000 as shown in table 4.3.

Table 4.3: Summary statistics for sodium levels before and after taking aminophylline, (N=188)

Variable	**Mean**	**Std.Dev**	***p*-value**
Serum sodium levels before	134.5	11.4	0.0000
Serum sodium levels after	128.7	9.31	

Figure 4.5 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

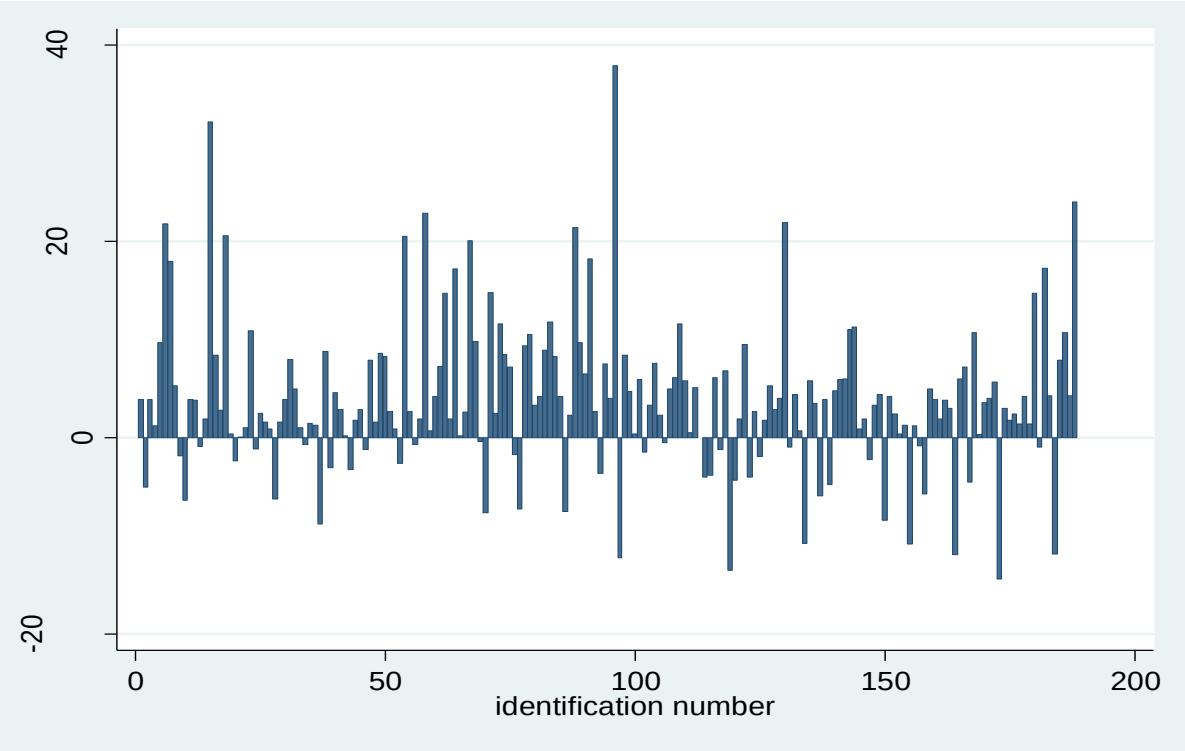

Figure 4.5: Two way bar showing the change in serum sodium levels after taking aminophylline by the participant ID (N=188)

Table 4.4 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 with *P*-value 0.0000.

Table 4.4: 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	4.90
diff = mean(sodium1)-mean(sodium2)				t = 6.8065	
Ho: diff = 0 Ha: diff>0 ; Pr(T > t) =0					

.

4.3 SOME FACTORS THAT MAY BE ASSOCIATED WITH HYPONATREMIA IN PREMATURE NEONATES ADMITTED TO NICU AT UTH

From table 4.5 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 4.5: 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

5.0 DISCUSSION

The present study discusses the prevalence rates of hyponatremia and effects of aminophylline on serum sodium levels in premature neonates admitted to NICU at UTH.
According to the findings the prevalence of hyponatremia in premature neonates was found to be at 51% from the 322 participants that were recruited. This prevalence is higher than what has been reported from other studies. Assadi 2012 in his clinical review reported the prevalence rates of hyponatremia in premature neonates to be at 29%. The highest prevalence was reported in India and United States of America at 29.8% and 30% respectively according to the studies conducted by marcialis et al. in 2011 and Upadhyay et al. in 2006. The difference could partly be attributed to the fact that, the prevalence from the above studies was reported from clinical reviews and case studies with a small patient population. The explanation is also in line with Upadhyay et al. 2006 who reported that the prevalence of hyponatremia varies, determined by a number of factors, including the definition of hyponatremia, frequency of testing, the healthcare setting, and the patient population. The current study looked at the prospective data and a cross sectional study design was used.
The present study found that the prevalence rates categorised by weight was highest in the low birth weight (less than 1.5kg) neonates than the ones above 1.5kg; this is in agreement with the findings by Al-Dahhan 1984 who also reported a lower prevalence of hyponatremia in neonates with normal birth weight.

The study further established that the majority of the premature neonates showed a significant decrease in serum sodium levels after taking a loading dose of aminophylline with *p*-value 0.0000. This is in line with the findings reported elsewhere. Mazkereth et al. 1997 loaded 19 premature infants with a mean gestational age of 31.1weeks with 6mg/kg aminophylline followed by maintenance therapy of 2mg/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. 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.

Modlinger et al. 2003 and Hocher (2010) linked the observed effect of aminophylline on the kidneys to the adenosine A_1 receptors. 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.

The findings by Hocher (2010) can possibly explain the significant reduction in the serum sodium levels that was observed in this study of premature neonates in NICU at UTH after a loading dose of aminophylline. The findings showed that the changes were significant with *p*-value 0.0000.

Among the factors that were found to be associated with hyponatremia in NICU at UTH in this 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 neonates and this was also reported by Field in 2010. 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. Marcialis et al. 2011, in his clinical reviews reported a hypertonic hyponatremia which he attributed to high glucose levels in the blood. There is enough clinical evidence to support these findings as suggested by Mitrovic-Jovanovic et al 2012, were they reported that resorption of water drawn by molecules like glucose (hyperglycemia in diabetes) lead to hyponatremia, thereby glucose being inversely related to serum sodium level.

CONCLUSION

From the study findings, it can be concluded on objective 1 that, the baseline prevalence of hyponatremia in NICU at UTH is 51%, and the prevalence rate was found to be highest among the neonates less than 1.5kg of weight. Therefore, the prevalence of hyponatremia in NICU at UTH is higher than the average global estimates.

The study on objective 2 further established that the majority of the premature neonates showed a decrease in serum sodium levels after taking a loading dose of aminophylline. This study showed that there was a significant difference in the serum sodium levels before and after aminophylline administration in premature neonates admitted to NICU at UTH with a *p*-value of 0.0000

In objective 3, the summary of the findings showed that, among the factors that were looked at in this study, it was established that weight, gestational age, RVD, RBS, age were associated with hyponatremia although, only weight and gestational age were significant.
In summary, the prevalence of hyponatremia in NICU at UTH is significantly high and using aminophylline in premature neonates lowers serum sodium levels and we propose use of sodium supplements. Nevertheless, the renal actions of aminophylline in premature neonates merit further investigation.

6.0 RECOMMENDATIONS

1. Serum sodium levels should be checked routinely in premature neonates admitted to NICU at UTH and there is need for a larger study that could address the correlation between serum sodium levels and clinical presentation.
2. There may be need for sodium supplements to neonates who are put on aminophylline in NICU at UTH.
3. This study suggests that weight and gestational age might be an important determinant in the calculation of the amount of sodium to supplement in premature neonates. The sodium supplementation can be based on the coefficient of linear regression as shown in the present study which indicates that, for every 1kg increase in weight serum sodium ions should be increased by 4mmol/l and for every 1 week increase in gestational age serum sodium ions should increase by 0.7mmol/l.

LIMITATION

1. The prematurity of the participants was a limiting factor, as the death rate in this group is quite high.
2. Since the study was done at the University Teaching Hospital, only high risk patients sent to the hospital were enrolled and this may not be a true reflection of the general population.
3. It is important to note that not all factors that can have an effect on serum sodium levels in premature neonates were considered for the study such as maternal exposure to steroids, hyperlipidemia, marked hyperproteinemia in the neonate etc.

REFERENCES

NICU treatment protocol 2010 Neonatal Intensive Care Unit University Teaching hospital Lusaka Zambia 2010 version.

NICU treatment protocol 2010.

NICU ward statistics 2012 Neonatal Intensive Care Unit University Teaching hospital Lusaka Zambia 2012 report.

ADEDOYIN, O. T., AKINDELE, J. A., AJAYI, A. & OKESINA, A. B. 2001. Serum electrolyte, urea and creatinine in clinically stable Nigerian newborn. *West African Journal Medicine,* 20**,** 263-7.

AHN, H. W., SHIN, W. G., PARK, K. J., SUH, O. K. & CHOI, J. H. 1999. Pharmacokinetics of theophylline and caffeine after intravenous administration of aminophylline to premature neonates in Korea. *Res Commun Mol Pathol Pharmacol,* 105**,** 105-13.

AL-DAHHAN, J., HAYCOCK, G. B., NICHOL, B., CHANTLER, C. & STIMMLER, L. 1984. Sodium homeostasis in term and preterm neonates. III. Effect of salt supplementation. *Arch Dis Child,* 59**,** 945-50.

AL QAHTANI, M., ALSHAHRANI, A., ALSKAINI, A., ABUKHALID, N., AL JOHANI, N., AL AMMARI, M., AL SWAIDAN, L., BINSALIH, S., AL SAYYARI, A. & THEABY, A. 2013. Prevalence of hyponatremia among patients who used indapamide and hydrochlorothiazide: A single center retrospective study. *Saudi J Kidney Dis Transpl,* 24**,** 281-5.

ASSADI, F. 2012. Hyponatremia: a problem-solving approach to clinical cases. *J Nephrol,* 25**,** 473-80.

BAAJAFER, F. S., HAMMAMI, M. M. & MOHAMED, G. E. 1999. Prevalence and severity of hyponatremia and hypercreatininemia in short-term uncomplicated hypothyroidism. *J Endocrinol Invest,* 22**,** 35-9.

COIMBRA, T. M., FRANCESCATO, H. D., BALBI, A. P., MARIN, E. C. & COSTA, R. S. 2012. Renal Development and Blood Pressure in Offspring from Dams Submitted to High-Sodium Intake during Pregnancy and Lactation. *Int J Nephrol,* 2012**,** 919128.

DAFTARY, A. S., PATOLE, S. K. & WHITEHALL, J. 1999. Hypertension-hyponatremia syndrome in neonates: case report and review of literature. *Am J Perinatol,* 16**,** 385-9.

FIELD, M. J. 2010. Comment on "Does 'asymptomatic hyponatremia' exist?". *Nat Rev Nephrol,* 6**,** 1.

HOCHER, B. 2010. Adenosine A1 receptor antagonists in clinical research and development. *Kidney International,* 78**,** 438-445.

HOHENSCHILD, S. & PAUST, H. 1993. [Seizures and hyponatremia in a newborn infant]. *Monatsschr Kinderheilkd,* 141**,** 110-1.

HSU, S. C. & LEVINE, M. A. 2004. Perinatal calcium metabolism: physiology and pathophysiology. *Semin Neonatol,* 9**,** 23-36.

KARBASI, S. A., MOSADEGH, M. M. & FALLAH, R. 2009. Utility of laboratory studies in seizures of children older than one month of age. *Singapore Med J,* 50**,** 814-6.

LOWRY, J. A., JARRETT, R. V., WASSERMAN, G., PETTETT, G. & KAUFFMAN, R. E. 2001. Theophylline toxicokinetics in premature newborns. *Arch Pediatr Adolesc Med,* 155**,** 934-9.

MARCIALIS, M. A., DESSI, A., PINTUS, M. C., IRMESI, R. & FANOS, V. 2011. Neonatal hyponatremia: differential diagnosis and treatment. *J Matern Fetal Neonatal Med,* 24 Suppl 1**,** 75-9.

MARCIALIS, M. A., DESSI, A., PINTUS, M. C., MARINELLI, V. & FANOS, V. 2012. Hyponatremia and hypernatremia in the newborn: in medio stat virtus. *Front Biosci (Elite Ed),* 4**,** 132-40.

MAZKERETH, R., LAUFER, J., JORDAN, S., POMERANCE, J. J., BOICHIS, H. & REICHMAN, B. 1997. Effects of theophylline on renal function in premature infants. *Am J Perinatol,* 14**,** 45-9.

MITROVIC-JOVANOVIC, A., DRAGOJEVIC-DIKIC, S., ZAMUROVIC, M., NIKOLIC, B., GOJNIC, M., RAKIC, S. & JOVANOVIC, T. 2012. Comparison of electrolytic status (Na+, K+, Ca2+, Mg2+) in preterm and term deliveries. *Clin Exp Obstet Gynecol,* 39**,** 479-82.

MODLINGER, P. S. & WELCH, W. J. 2003. Adenosine A1 receptor antagonists and the kidney. *Curr Opin Nephrol Hypertens,* 12**,** 497-502.

MORITZ, M. L. & AYUS, J. C. 2009. Hyponatremia in preterm neonates: not a benign condition. *Pediatrics,* 124**,** e1014-6.

NG, G. Y., BAKER, E. H. & FARRER, K. F. 2005. Aminophylline as an adjunct diuretic for neonates--a case series. *Pediatr Nephrol,* 20**,** 220-2.

NOGUCHI, T., HAYANO, Y., IWASAKA, H., SETOGUCHI, K., ODA, S., TANIGUCHI, K., HONDA, N., MORI, Y. & HADAMA, T. 1990. [Diuretic effects of aminophylline in patients after cardiac surgery]. *Masui,* 39**,** 1002-6.

PRETZLAFF, R. K., VARDIS, R. J. & POLLACK, M. M. 1999. Aminophylline in the treatment of fluid overload. *Crit Care Med,* 27**,** 2782-5.

SUHARDJONO 2011. Hyponatremia, prevalence, diagnosis, and management. *Acta Med Indones,* 43**,** 149-51.

THOMAS, T. C., SMITH, J. M., WHITE, P. C. & ADHIKARI, S. 2012. Transient neonatal hypocalcemia: presentation and outcomes. *Pediatrics,* 129**,** e1461-7.

UPADHYAY, A., JABER, B. L. & MADIAS, N. E. 2006. Incidence and prevalence of hyponatremia. *Am J Med,* 119**,** S30-5.

ZANARDO, V., GIACOBBO, F., ZAMBON, P., TREVISANUTO, D., GRIFFITH, P., GRELLA, P. & ZACCHELLO, G. 1990. Antenatal aminophylline and steroid exposure: effects on glomerular filtration rate and renal sodium excretion in preterm newborns. *J Perinat Med,* 18**,** 283-8.

APPENDIX I

INFORMATION SHEET

Invitation

You are invited to participate in this study that is looking at the levels of Sodium and the problems drugs like aminophylline can give to the babies.

NATURE AND PURPOSE OF THE STUDY

The problem is that, premature neonates tend to have low levels of sodium because of the prematurity of the kidneys. This study will help the paediatricians to manage the premature babies better.

PROCEDURES OF THE STUDY

If you accept to participate in the study, information on your antenatal period and the delivery as well as on your baby will be collected. Blood will be collected as part of care and then you will be informed of the findings.

POSSIBLE RISKS AND DISCOMFORT

Your baby will not be exposed to any known risks by enrolling into the study. Electrolyte testing as is done in the hospital on patients is not known to be dangerous or harmful to any part of the human body. Your baby will be looked after on the ward by the attending doctors like any other baby admitted to the ward.

POSSIBLE BENEFITS

Your baby will benefit in that if there is any problem with the levels of sodium then it will be corrected. Sodium is a mineral needed for a child to grow healthy and gain weight, so if we know the levels it will help the doctor to treat your child and recover in weight gain faster and make your child health.

CONFIDENTIALITY

All information collected in this study is strictly confidential and data or information that will be collected and reported will not include your names.

CONTACT INFORMATION

If you have any questions or concerns please contact: The Principle investigator Mr Mukosha Moses Email address: mukoshamoses@yahoo.com, cell: 0979322353 or the Ethics committee chairperson ERES converge IRB Dr. Esther Munalula-Nkandu Email: eresconverge@yahoo.co.uk cell: +260966765503

APPENDIX II

CONSENT FORM

I…….. have been invited to take part in the study that is looking at levels of sodium and the problems drugs like aminophylline can give to the babies. I have read the information, or it has been read to me and I voluntarily consent to have my child participate in the study. I understand that I have the right to withdraw from the study at any time without affecting the care of my child and that I will be given no special services or any payments or gifts.

…….. ……/…../…..

Signature/ thumb print of participant Date

……. ……/…../…..

Name/signature of witness Date

…… ……/…../…..

Name/signature of researcher Date

APPENDIX III

QUESTIONNAIRE FOR THE MOTHER

1. Identity No ……..
2. Age: …….
3. Parity: ……..
4. Gravidity……..
5. Home address----------
6. Employment status---------- □
7. History of neonatal deaths: 1.Yes □ 2. No□

   If yes, what was the cause: ……..
8. RVD status----------

APPENDIX IV

LABORATORY FORM FOR THE NEONATE

Identity No ……..

Reason for admission ----------

Gestational Age:……..

Birth weight:……

Sex:----------

Age----------

Sodium levels----------

Blood glucose level----------

RVD status----------

Receiving Aminophylline Yes/No

If yes, sodium levels----------

Published Articles

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.

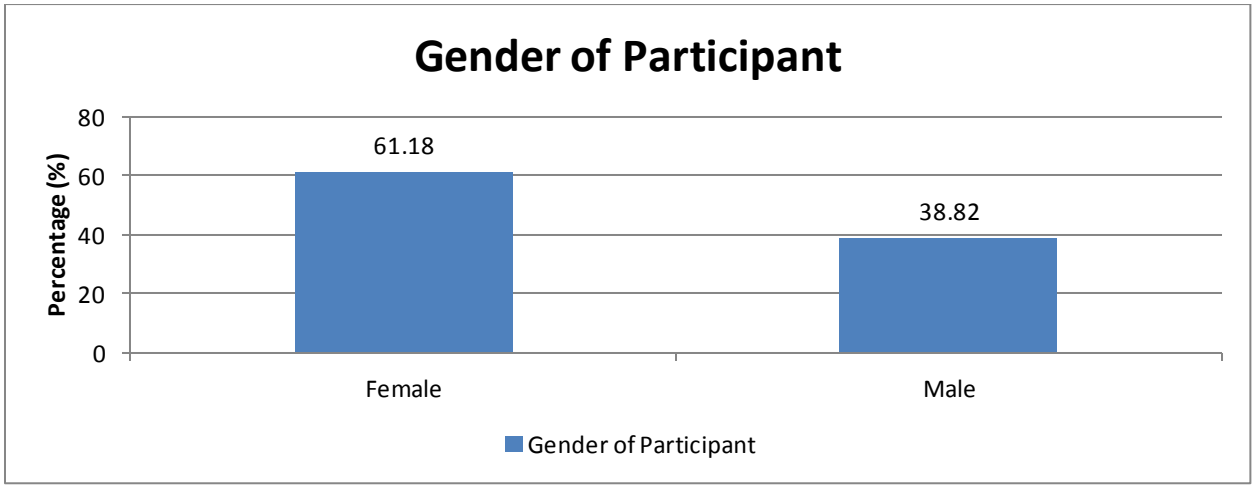

Figure 1: Gender distribution of Participants

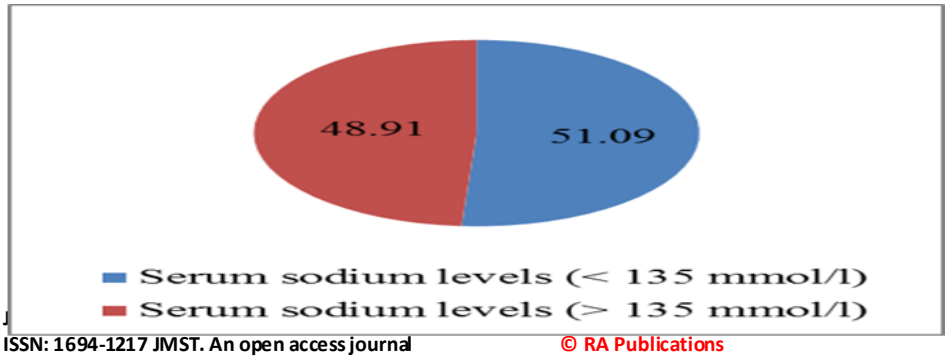

Figure 2: Baseline Prevalence (%) of hyponatremia in premature neonates admitted to NICU at UTH

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.

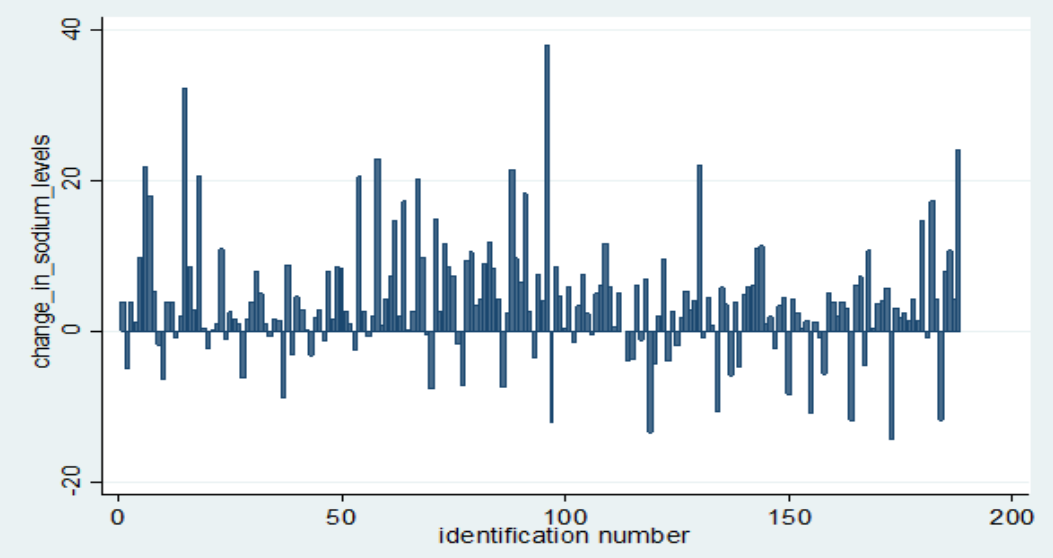

Figure 3: Two way bar showing the change in serum sodium levels after taking aminophylline by the participant ID (N=188).

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.

