PREVALENCE AND RISK FACTORS FOR HYPERNATREMIA IN SEVERELY DEHYDRATED INFANTS AT KENYATTA NATIONAL HOSPITAL.

This dissertation has been written in part fulfillment of the degree of Master of Medicine in Pediatrics and Child Health of the University of Nairobi.

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DECLARATION

I declare that this dissertation is my original work and has not been presented to any other university for a degree.

Signed _____ Date 16.11.06

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This dissertation has been submitted with our approval as the university supervisors.

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ACKNOWLEGEMENTS

I most sincerely wish to thank the following,

1. My supervisors - Dr Irimu, Prof. Macharia and Dr Amayo for their patient guidance and critical appraisal of the writing of this project, right from proposal level to completion. To them, I am greatly indebted.

2. My assistant Mr. Goeffrey Orina who spent many hours with me, patiently screening and recruiting the infants in this study.

3. The members of staff in the pediatric filter clinic for their co-operation and encouragement.

4. Mr. Raymond Musyoka - NARESA, for assistance with data analysis.

5. Lords healthcare for logistic support during data collection.

6. My parents for their encouragement and support during my studies and especially during the data collection period.

7. Last but not least, to the caretakers and the infants who participated in this study, without whom, this study could not have been carried out.

DEDICATION

This work is dedicated to my husband Bernard and children Alex and Anita, who have patiently borne my long absences from them.

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SUMMARY

Background

Hypernatremia is associated with a mortality rate ranging from 15% to 60%, residual brain deficits, hypertonia and convulsions. Prevalence of hypernatremia in severely dehydrated infants has not been well described previously.

Objectives

A case control study was done to determine prevalence of hypernatremia in severely dehydrated infants at Kenyatta National Hospital, risk factors for hypernatremia in severely dehydrated infants and to document early adverse clinical outcomes in infants with hypernatremic dehydration.

Methodology

Serum sodium levels of severely dehydrated infants were determined. Infants presenting with hypernatremia were recruited as cases. Controls were infants with normal sodium levels and those with hyponatremia. Characteristics of cases and both controls were compared to determine risk factors for hypernatremia. Early adverse clinical outcomes in the study population were documented by clinical re-evaluation during the first seven days following admission.

Results

Of the 936 severely dehydrated infants who were reviewed, 55 had hypernatremia and comprised the cases. The prevalence of hypernatremia was 5.9% (95% C.I = 3.5% – 6.5%). An equal number of controls were selected from infants with isonatremia and those with hyponatremia.

In a multivariate comparison of cases with isonatremic and hyponatremic infants, cases had a greater than 12 fold likelihood of vomiting more than eight times in a

day (72.7% compared to 21.8% and 18.2%, p value < 0.001 for both controls), and a 2.4 fold increased chance of a rectal temperature greater than 38.5^{0}C (70.9% compared to 40% and 36.4%, p value < 0001) for both controls. Cases had a three fold greater likelihood of having a mean temperature of 38.5^{0}C as compared to isonatremic controls (O.R 3.2 95% C.I 1.7 – 5.8, p value < 0.001). In addition, cases were more likely to report excessive sleepiness and vomiting everything ingested as compared to isonatremic infants (O.R 4.5, 95% C.I 1.5 – 13.4, p value = 0.005 and O.R 15.4 95% C.I 4.4 – 54.2, p value < 0.001 respectively).

Cases were significantly less likely to have used plain water compared to both controls (20% compared to 54.5% and 36.4%, p values = 0.008 and 0.01 respectively).

Cases had a three fold higher likelihood of adverse outcome as compared to isonatremic controls (72.9% compared to 41.8%, O.R 3.3, 95% C.I 1.1 – 8.1 p value= 0.05). Cases were two and a half times more likely to have an adverse outcome compared to hyponatremic controls. This finding was not statistically significant (O.R 2.5, 95% C.I 0.99 – 5.1, p value = 0.06). In the three study groups, statistically significant differences were observed in the proportions of infants who survived, on comparison of those who presented in deep coma with those who did not (p value< 0.001 for hypernatremic and hyponatremic infants and p value = 0.01 for isonatremic infants).

Conclusions

Severely dehydrated infants who have; excessive vomiting, excessive sleepiness, or a rectal temperature greater than 38.5^{0}C, should be considered at a high risk of having hypernatremia and thus prioritized for determination of serum sodium level. This will improve detection of hypernatremia and facilitate management using appropriate rehydration plans.

INTRODUCTION AND LITERATURE REVIEW

Hypernatremia, a serum sodium level greater than 145 millimoles per liter (mmol/l) is commonly the product of inadequate free water intake, pure water loss exceeding sodium loss, or iatrogenic sodium loading (1,2). Whereas hyponatremia may be physiologic in certain edematous states, hypernatremia is usually associated with hyperosmolality and should always be considered abnormal (3, 4).

Sodium is the bulk cation in the extra cellular fluids and is the principal osmoticaly active solute responsible for maintenance of intravascular and interstitial volumes. Sodium helps regulate polarization of cell membranes and provides the ionic milieu in which biologic reactions take place. Normal serum sodium levels range from 135 to 145 mmol/l (5).

The body has two defense mechanisms to protect against hypernatremia; the ability to produce concentrated urine and a powerful thirst mechanism. Arginine vasopressin or antidiuretic hormone (ADH) is synthesized in the supraoptic and paraventricular nuclei of the hypothalamus and secreted by the posterior lobe of the pituitary gland. Release of ADH occurs when the plasma osmolality exceeds 275 milliOsmoles per kilogram. ADH promotes reabsorption of water in the renal tubules, producing concentrated urine and facilitating the maintenance of a normal serum sodium concentration (1,3,5).

Hypernatremia induces intense thirst and this is the body's second line of defense. Thirst provides the ultimate protection against hypernatremia by encouraging free water intake (1,3,5). The patients at greatest risk for hypernatremia are those having either, impaired thirst mechanism as occurs with ageing, an altered mental status or are unable to access water due to developmental or physical limitations (3,4).

Significance of hypernatremia

The contribution of electrolyte imbalance to childhood morbidity and mortality has been documented from as far back as 1947 though existence of hypernatremia has been recorded since 1805. A review of the data collected then showed a positive correlation between increasing sodium levels and infant morbidity (6). Known complications of hypernatremia usually involve the central nervous system and include; convulsions, hypertonia, hemiplegia, and residual brain deficits. (1, 2, 3, 5) Residual brain damage has been reported in ten to fifteen percent of children who survived hypernatremic dehydration (3, 6). In other studies, permanent neurological sequelae have been recorded on long-term follow up in thirty percent of patients who survive acute hypernatremic dehydration. (7, 8).

Mortality associated with hypernatremia in children has been variably quoted as ranging between 15 to 60%, depending on the patient population examined. Higher mortalities occur in infants with inadequate or delayed correction of hypernatremia (1, 2, 9,10). Co - morbidity contributes significantly to mortality associated with hypernatremic dehydration (8, 10).

Morbidity and mortality associated with hypernatremia may result from the pathophysiological changes that occur in the brain in response to hypernatremia or from inappropriate management of this condition. Within minutes after the development of hypertonicity, which accompanies hypernatremia, loss of water from brain cells causes shrinkage and an increase in intracellular osmolality. A rapid adaptation response occurs within a few hours as electrolytes enter the brain cells with resultant partial restitution of brain volume (2). In acute severe hypernatremia the brain cells may not accumulate electrolytes fast enough to preserve volume, resulting in shrinkage and physical separation of the brain from the meninges and rupture of the bridging veins. This causes intracerebral and intracranial hemorrhage and may result in death (3).

In the presence of ongoing hypernatremia, normalization of brain volume is completed within several days as a result of the intracellular accumulation of organic osmolytes. In laboratory animals these osmolytes have been identified as myoinositol, N-acetylaspartate, choline, and taurine. This is termed as the slow adaptation response. The high intracellular osmolality persists despite the normalization of brain volume. When slow correction of the hypertonic state is instituted, it reestablishes normal brain osmolality without inducing cerebral edema, as the dissipation of accumulated electrolytes and organic osmolytes keeps pace with water repletion (2, 8).

In contrast, rapid correction of hypernatremia may result in convulsions due to cerebral edema, which occurs when water uptake by brain cells outpaces the dissipation of accumulated electrolytes and organic osmolytes. Cerebral edema is associated with the risk of permanent neurological impairment and death. It follows therefore, that detection of hypernatremia at the earliest opportunity and proper management, would contribute to a lowering of the associated morbidity and mortality (2, 8, 10).

Infants with hypernatremia may present with increased muscular tone, nuchal rigidity, tonic-clonic seizures or coma (2, 3). However, some dehydrated children with significant hypernatremia have been observed to have no specific clinical predictors of this derangement, and would hence only be identified by laboratory evaluation (11). Evaluation of laboratory tests done in dehydrated children indicated that attending physicians had a low sensitivity (58%) in detecting dehydrated children with a significant electrolyte abnormality, when relying on clinical evaluation alone. A serum sodium level is therefore necessary in patients at risk of hypernatremia, especially where intravenous fluid therapy is anticipated (12,13,14).

Prevalence and risk factors for hypernatremia.

Prevalence of hypernatremia varies with the population studied. Lactational failure is a documented risk factor for hypernatremic dehydration in neonates. Oddie et al examined neonates readmitted within the first month after delivery with hypernatremia and found them to be severely dehydrated with an average weight loss of fifteen percent (15). There are many other reports of neonates who develop hypernatremia in the immediate post-natal period (16–19). The underlying problem in all these studies was consumption of inadequate amounts of breast milk resulting in severe hypernatremic dehydration as the free water losses exceeded sodium loss. Under these circumstances the prevalence is estimated at ten to thirty percent (20, 21).

Infants are at particularly high risk for the development of hypernatremia because of their relatively large surface area to volume ratio and their dependency on a caretaker to administer fluids (8,9). The interventions by caretakers of dehydrated children are influenced by the guardian's own age, level of education and experience in the care of children (22, 23).

Hospitalized patients are at particular risk for hypernatremic dehydration due to inadequate free water administration especially if they are obtunded or intubated and fully dependent on others for their water requirements. Water needs may be higher in disease states than in health and patients may be unable to express this need (9,10). Acidotic patients requiring resuscitation are at risk for hypernatremia due to excessive sodium bicarbonate administration (1,2,10). The prevalence of hypernatremia in hospitalized patients has been reported variably as one to three percent and affects patients of all age groups (24, 25). In both children and adults the prevalence of hypernatremia has been found to be higher in hospitalized patients than in out patients (25, 26). At Kenyatta National Hospital (KNH), unpublished data indicates that the in patient mortality from gastroenteritis, a known risk factor for hypernatremia, averages 20%.

Fifty percent of all mortality in children at KNH occurs within the first 24 hours (27). The contribution of severe dehydration and hypernatremia to this mortality can not be determined at present, as a serum sodium level is not routinely done in severely dehydrated children. One out of five children who present at the pediatric filter clinic in KNH is severely dehydrated. Of those attended to at the pediatric filter clinic (PFC), 58% are infants (28).

Hawkins studied both inpatients and out patients in Singapore and noted that though there were more males in both hyper and hyponatremic groups, the male gender was not a risk factor for hypernatremia (26).

Swingler and Powers working in Cape Town noted seasonal fluctuations in the prevalence of hypernatremia in dehydrated children. The prevalence in summer was less than one percent as compared to a peak of five percent in winter. Finberg, close to two decades earlier had noted an increase in cases of hypernatremic dehydration during the winter months. A similar finding was also reported in Egypt. It is postulated that an increase in rotavirus associated diarrheal disease in winter contributed to these observations (25, 29, 30).

The prevalence of hypernatremia has been found to vary with location even within the same country. Ongeri working in Nairobi recorded a prevalence of eight percent in the out patients presenting with dehydration while Kirika recorded a prevalence of thirty nine percent in children with a similar presentation at the Kenyan coastal town of Mombasa (31, 32). The high sodium concentration found in the drinking water at the coast was presumed to have predisposed these children to hypernatremic dehydration (32).

High sodium intake in poorly reconstituted preparations such as conventional oral rehydration salts (ORS), home made salt sugar solutions and formula feeds has been identified as a risk factor for hypernatremia in United States of America, Egypt, and Zimbabwe (22,30,33,34). In Egypt, among 60% of dehydrated children who had

used ORS, three to seventeen percent developed hypernatremia. On further evaluation it was found that the guardians of these children used water proportions that were much lower than recommended, to reconstitute these solutions (30, 33). Nathoo et al in Zimbabwe found a positive correlation between occurrence of hypernatremia and use of homemade salt and sugar solutions (34). During childhood illnesses, practices such as starving a child of food and fluids greatly increase the risk of developing hypernatremia (35,36). The 2003 Kenya Demographic and Health survey indicates that 26% of children less than five years receive much less or no food and fluids at all during a diarrheal episode, which puts them at risk for severe dehydration and malnutrition (37).

Gastroenteritis, a combined diagnosis of diarrhea and vomiting is a well-documented risk factor for hypernatremia especially when it continues for five to seven days with inadequate free water replacement. Recent studies in developed countries show that it is a much less common cause of hypernatremia than previously reported (5,10).

Migiro and Wassuna who studied electrolyte changes in children having diarrhea only at KNH recorded hypernatremia prevalences of two and one percent respectively. A previous study, which included children who had dehydration either due to diarrhea with or without other illnesses recorded a prevalence of eight percent (31, 35, 38). The difference in these observations may be due to the fact that diarrhea causes loss of both water and sodium, usually resulting in isonatremic dehydration while the presence of emesis, fever and tachypnea as occurs with other illnesses increases free water losses and predisposes to hypernatremia (39).

Febrile illnesses contribute to the occurrence of high serum sodium levels by increasing metabolic needs of the body and insensible water losses through the skin by sweating, hence increasing the requirements for water.
Tachypnea and mechanical ventilation also increase insensible water losses from the respiratory tract (4).

A higher prevalence of hypernatremia has been recorded in studies, which include patients who suffer febrile illnesses compared to those, which did not (31, 35, 38).

Severe dehydration is a common complication of childhood illnesses and a leading cause of morbidity and mortality, which is estimated to contribute to 14 to 30% of deaths in children aged less than five years of age (40 – 44). Severe dehydration results when fluid losses exceed fluid intake and may be associated with electrolyte imbalance, commonly involving sodium, potassium and hydrogen as a result of unequal losses of water and electrolytes (5). Evaluation of laboratory tests done in children having clinical features of dehydration indicates that severity of dehydration has a positive correlation with increase in serum sodium levels, hence severe dehydration is a risk factor for hypernatremia (2, 5, 12 - 14, 39, 45).

STUDY JUSTIFICATION

Kenyatta National hospital is a regional referral center, and hence more likely to receive patients with complicated illnesses. However a serum sodium level is not routinely determined for dehydrated patients, due to scarcity of resources. There is need to identify risk factors for hypernatremia that would guide clinicians in identifying infants who would benefit most from serum sodium level determination.

Hypernatremic dehydration is associated with significant mortality and a higher risk of neurological sequelae compared to non – hypernatremic dehydration. Morbidity may be averted by the correct choice and flow rate of intravenous fluids.

Infants are at a greater risk of developing hypernatremia and it would be especially useful to determine the prevalence of hypernatremia in this group of patients.

Early adverse clinical outcomes in severely dehydrated infants with hypernatremia in Kenyatta national hospital have previously not been described, this was undertaken

to determine the impact hypernatremia has on severely dehydrated infants at Kenyatta national hospital.

OBJECTIVES

PRIMARY OBJECTIVES

1. To determine prevalence of hypernatremia in severely dehydrated infants at Kenyatta National Hospital.

2. To determine risk factors for hypernatremia in infants at Kenyatta National Hospital.

SECONDARY OBJECTIVE

To describe early adverse clinical outcomes of infants with hypernatremic dehydration.

METHODOLOGY

STUDY DESIGN

This was a hospital based case control study.

STUDY AREA

The study subjects were recruited from the pediatric filter clinic (PFC) of the Kenyatta National Hospital, a national referral and teaching hospital located in Nairobi, Kenya. The PFC serves as the emergency reception for all sick children less than 13 years of age who present at this hospital.

On average 5000 children are attended to at the PFC on a monthly basis, 1000 of who are severely dehydrated. Infants form 58% of those attended to at the PFC.

Kenyatta National Hospital has an inpatient bed capacity of 1868 beds, 335 of which are in the four pediatric general wards from where those who were admitted were followed up. Kenyatta National Hospital also serves as the teaching hospital for the University of Nairobi.

STUDY DURATION

Data collection was carried out for 15 weeks, from 20th June 2005 to 23rd September 2005.

INCLUSION CRITERIA

1. Informed written consent to participate in the study, provided by the guardian.

2. Infants with severe dehydration as determined by the WHO classification, (appendix 1) aged one to twelve months. Where one month was taken to be a complete calendar month.

CASES

These were severely dehydrated infants with a serum sodium level greater than 145 mmol/l.

CONTROLS

Two controls groups were selected from the severely dehydrated infants with a serum sodium level equal to or less than 145mmol/l. One group of controls was selected from hyponatremic infants and the other from isonatremic infants.

EXCLUSION CRITERIA

Infants who presented at PFC while already on intravenous fluids and those who had received sodium bicarbonate in the referring facility. These interventions would have interfered with serum sodium levels.

SAMPLING METHOD

Severely dehydrated infants aged one to 12 months were identified and blood samples taken for serum sodium level determination. Those with a serum sodium level greater than 145 mmol/l were recruited sequentially as study cases. The prevalence of hypernatremia in KNH from previous studies was 8%, which meant that one out of 13 dehydrated patients was likely to have hypernatremia. From the patients without hypernatremia, two controls were recruited for each hypernatremic patient by selecting every sixth patient from those with a serum sodium level within the reference range and the sixth patient from those with a serum sodium level less than 135 mmo/l. This was done to minimize bias. Where the sixth patient was not eligible for inclusion then the seventh one was selected. Both isonatremic and hyponatremic controls were selected due to expected differences in characteristics and adverse clinical outcomes in comparison with hypernatremic infants.

SAMPLE SIZE CALCULATION

Using the formula: (46)

$$N = (z_{1-\alpha/2}\sqrt{[2p_2(1-p_2)]} + z_{1-\beta}\sqrt{[p_1(1-p_1) + p_2(1-p_2)]})^2 \quad /(p_1 - p_2)^2$$

p_1 = Proportion of children who developed hypernatremia following homemade salt sugar solution use. (Rounded off to 10%)

α = the type 1 error corresponding to 5%.

$1 - \beta$ was the power of the study = 80%

N = 51.

CLINICAL PROCEDURES

The investigator and a trained nurse visited the pediatric filter clinic every weekday between 10 00 hours and 20 00 hours during the study period. Severely dehydrated infants aged one to twelve months were identified by physical examination during which the degree of dehydration was determined using the WHO assessment chart (appendix 1). The guardians of the severely dehydrated patients were informed about the study and consent was sought. Guardians indicated their consent to participate by signing a consent form (appendix 2).

An intravenous cannula was established after the puncture site was cleaned using 70% alcohol. A venous blood sample for serum sodium level was obtained from the intravenous access by allowing two milliliters to run into a plain bottle, before fluid therapy was started. The blood sample was immediately taken to the main biochemistry laboratory in KNH.

The laboratory results were communicated to the attending clinician as soon as they were received and also recorded in the data collection sheet. Those who were recruited as cases and controls had the full questionnaire administered.

Demographic data of the child including name, age in months, sex and vital signs were recorded. These vital signs included blood pressure, rectal temperature in degrees centigrade, respiratory and pulse rates. The weight and the length were also taken.

Rectal temperature was taken using a low reading digital thermometer, while systolic and diastolic blood pressure measurements were done using an appropriate blood pressure cuff. The respiratory and pulse rates were counted over one minute timed using a stopwatch. The weight was taken using an electronic top pan balance machine (Soehnle and Muller Gmb Germany) and recorded to the nearest 50 grams. The infants' length was taken using a measuring board. Blood pressure, weight and length measurements were taken twice and the average obtained. This data was recorded on the precoded data collection sheet (appendix 3). The modified Glasgow coma scale (appendix 4) was used to determine the level of consciousness.

Presenting complaints in particular diarrhea, vomiting, hotness of body, convulsions, excessive sleepiness, and refusal to feed were sought. The guardian's interventions in response to the infant's illness were also recorded. These included withholding feeds, administration of conventional ORS, homemade salt sugar solutions, herbal medicine, plain water, cow's milk or prior health facility visits. The presumptive diagnosis made by the attending clinician was also recorded.

LABORATORY PROCEDURES

Serum sodium level was measured by an indirect-reading, ion-selective, electrode potentiometry machine (Olympus AU 400 Olympus corporation, Japan linear range 30 - 200mmol/l). The indirect reading electrode potentiometry method involves dilution of the specimen with a buffer prior to electrode contact. This method reliably detects sodium concentrations between 30 and 200 mmol/l. Specimen dilution is recommended when values above 200mmol/l are obtained.

Calibration was done every morning before any study samples were analyzed. Commercial quality control materials at low, normal and high sodium concentrations were used to assess the effectiveness of the calibration. Study samples were only run when the quality control values were within acceptable limits (± two standard deviations of the manufacturer's target value).

DOCUMENTATION OF OUTCOMES

Documentation of adverse outcomes in the study population was done by review of the patients' records and clinical status. Outcomes of interest included; hypertonia, convulsions, an altered level of consciousness, and death. Discharge from the wards or PFC without any of these events was recorded as an uneventful recovery. Those admitted to the pediatric general wards were followed up to a maximum of seven days.

During admission the patients underwent treatment at the attending clinician's discretion. Serial measurements of the serum sodium levels were beyond the scope of this study.

DATA MANAGEMENT

All the data collected on the precoded data sheets was entered into a personal IBM™ computer and analyzed using the statistical package for social sciences (SPSS™) version 10, S plus™ and the Epi info version 6™ programs.

Data was summarized using mean, mode and median, then presented in form of tables, and graphs as appropriate.

Prevalence of hypernatremia in severely dehydrated infants aged one to twelve months was calculated as shown below:

$$\frac{\text{Total number of infants with hypernatremia}}{\text{Total number of infants with severe dehydration}} \times 100 \text{ population}$$

Confidence interval around estimates was computed using the following formula:

$$95\% \text{ confidence interval, C.I} = P +/- 1.96 \times Se(p)$$

$$Se(p) = \sqrt{pq/n}$$

Where p = 0.05, q = 1- p = 0.95, and n was the study population.

Odds ratios (O.R) for the various risk factors were determined by logistic regression analysis. Ninety five percent confidence intervals (95% C.I) around the odds ratios were computed and an interval excluding unity (one) was taken to be significant. A p value less than 0.05 was also taken to be significant. Multivariate analysis was done for statistically significant risk factors.

Outcome measures were described in terms of proportions and odds ratios were also determined.

Cox regression analysis was used to compare differences in the survival probability between cases and each control group.

ETHICAL CONSIDERATIONS

Approval to carry out the study was sought and garnted from the Kenyatta National Hospital Ethics and Research committee.

A written consent form (appendix 2) was given to the guardians of infants eligible for inclusion into the study, who read through it with the help of the investigator where required. The guardian was allowed to ask questions before signing the consent form, and a venous blood sample was only taken after consent was obtained.

Emergency care and resuscitation were a priority to any procedure that was a part of the study. The intravenous access established by the investigator was used to withdraw the blood sample and for intravenous therapy.

The principal investigator was not involved in the care of the study patients. Relevant information obtained was given to the attending clinician to help in patient management. The subjects were free to withdraw from the study at their wish without any penalties.

RESULTS

PREVALENCE OF HYPERNATREMIA.

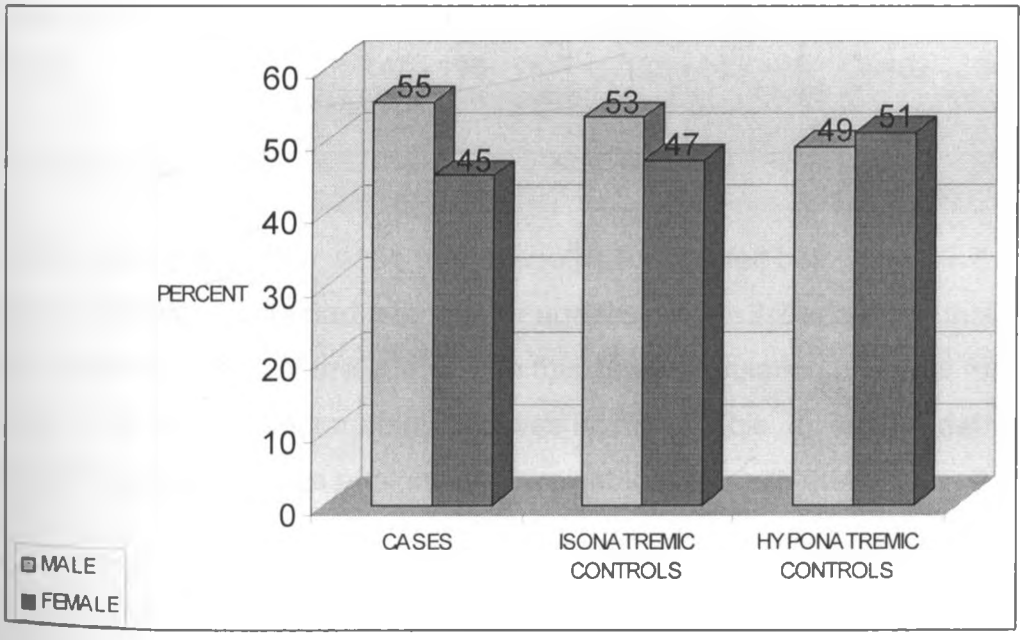
During the study period, a total of 936 infants aged between one and twelve months were classified as having severe dehydration. Fifty-five of these had hypernatremia while 497 (53.2%) had hyponatremia. There were 384 (40.9%) infants with a serum sodium level within the normal range. The serum sodium level among the severely dehydrated infants and in the study population ranged from 102 to 198 mmol/l.

The prevalence of hypernatremia in severely dehydrated infants at Kenyatta National Hospital was 5.9% (95% C.I = 3.5% to 6.5%).

CHARACTERISTICS OF THE STUDY POPULATION

The gender distribution was similar in all the study groups, as shown in Figure 1 below.

Figure 1: Sex distribution of the study population.



The difference in the sex distribution between cases and isonatremic controls, and between cases and hyponatremic controls was not statistically significant (O.R 0.93, 95% C.I. 0.44 – 1.97, p value = 0.85 and O.R 0.8, 95% C.I 0.38 – 1.7, p value = 0.57 respectively). No association was observed between gender and hypernatremia.

Table 1 below shows baseline characteristics recorded for the three groups of patients. The only statistically significant difference was observed in the mean serum sodium level.

Table 1: Baseline characteristics of the study population.

Variable	**Hypernatremic n = 55**	**Isonatremic n = 55**	**Hyponatremic n = 55**	**p value**
Age (months) Mean S.D	6.6 ±3.3	6.2 ±3.7	6.7 ± 3.4	0.74
Length for age mean z scores, S.D	-0.28 ± 0.89	-0.15 ± 0.6	- 0.12 ± 0.74	0.65
Sodium level (mmol/l) Mean, S.D Range	154.3 ± 7.1 147 - 198	138 ± 3.0 135 - 145	123.1 ± 7.7 102 - 134	<0.001*

*Statistically significant

In this study population, none of the lengths for age fell below the –3 Z score. Two hypernatremic infants had a length for age less than -2 Z score but this finding was not observed in any of the controls. In this study population a weight for height Z score analysis to detect malnutrition was not applicable, as severe dehydration had caused varying degrees of significant weight loss in each infant.

CHARACTERISTICS OF THE HYPERNATREMIC PATIENTS.

Among the 55 hypernatremic infants, there were 30 male patients (54.5%) and 25 female patients (45.5%). The age ranged from one to twelve months, with a mean age of 6.6 (S.D ±3.3) months and a median age of six months.

The mean length was 66.3 (S.D ± 7.7) centimeters. Two infants had lengths for age that fell below the – 2 Z score and no length fell below the –3 Z score.

The mean Glasgow coma scale (GCS) rating among hypernatremic infants was 9 (S.D ± 2.38). An abnormal GCS was observed in 54 (98.2%) infants on presentation.

The three most frequent complaints raised by the guardians of hypernatremic infants were refusal to feed, vomiting and fever, which occurred in 87.2%, 85.5% and 67.3% of the infants respectively.

Pneumonia was the most frequent clinical diagnosis made at PFC among the cases (45.5%), while gastroenteritis, meningitis, cerebral palsy and malnutrition were the next most frequent, at 27.3%, 20.0%, 9% and 7.2% respectively.

CHARACTERISTICS OF THE CONTROL POPULATION.

Among the isonatremic infants, there were 29 male patients (52.7%) and 26 female patients (47.3%), while among hyponatremic controls there were 27 male patients (49.0%) and 28 female patients (51.0%).

In both groups of controls, the age ranged from one to twelve months, with mean ages of 6.2 (S.D ± 3.7) months and 6.7 (S.D ± 3.4) months among isonatremic and hyponatremic controls respectively. A median age of seven months was observed among both isonatremic and hyponatremic controls.

The mean length among isonatremic infants was 65.8 (S.D ± 9.0) centimeters while that among hyponatremic controls was 67.1 (S.D ± 7.5) Centimeters. None of the lengths for age fell below the – 2 Z score.

The mean GCS rating among isonatremic infants was 11 (S.D ± 2.3) while that among hyponatremic infants was 10 (S.D ± 2.3). An abnormal GCS was observed in 52 (94.5%) isonatremic infants and 54 (98.2%) hyponatremic infants.

Vomiting was the most frequent presenting complaint reported by guardians of isonatremic infants and was observed in 89% of them. Refusal to feed and diarrhea were the next most frequent both of which were reported by 67.2% of the guardians. Among the hyponatremic controls, diarrhea and refusal to feed were the most frequent complaints both of which were reported by 76.4% of the guardians. The next most frequent complaint was vomiting (72.7%).

Pneumonia was the most frequent diagnosis among both isonatremic and hyponatremic controls with frequencies of 47.2% and 45.5% respectively. The next most frequent diagnosis in both groups was gastroenteritis reported at frequencies of 32.7% and 21.8% respectively. A diagnosis of meningitis was made in 10.9% of the isonatremic infants and 14.5% of the hyponatremic ones.

RESULTS OF UNIVARIATE ANALYSIS OF RISK FACTORS FOR HYPERNATREMIA:

I. CLINICAL PARAMETERS

Table 2: Comparison of clinical parameters between cases and isonatremic controls.

Variable	Cases n = 55		Isonatremic n = 55		O.R	95%C.I	p value
Age (months) Mean, S.D	6.6	±3.3	6.2	±3.7	1.0	0.9 – 1.2	0.54
Length for age (Cm) mean z score, S.D	-0.28	± 0.89	-0.15	± 0.6	0.7	0.6 – 1.0	0.75
Temperature (°C) Mean, S.D	38.5	± 4.2	38.0	±1.2	1.98	1.4 – 2.8	<0.001*
> 38.5°C (no. %)	39	70.9	22	40.0	3.6	1.6 – 8.4	0.02*
Respiratory rate (cycles/min) Mean, S.D	55.0	±16.0	51.0	± 13.0	1.02	0.9 – 1.0	0.12
Systolic blood pressure (mmHg) Mean, S.D	99.7	±4.7	94.12	±6.0	1.2	1.1 – 1.18	0.01*
High# (no. %)	8	14.5	6	10.9	1.0	0.9 - 1.9	0.75
Diastolic blood pressure (mmHg) Mean, S.D	59.4	±5.2	57.3	±9.7	1.04	0.97 – 1.1	0.33
Low# (no. %)	2	3.6	4	7.2	0.48	0.3 – 1.0	0.67
Pulse beats per min Mean, S.D	123	±19.8	120	±20	1.0	0.9 – 1.0	0.43
Glasgow coma scale Mean , S.D	9	± 2.4	11	± 2.3	1.2	0.9 – 1.2	0.8

*Statistically significant

A high systolic blood pressure fell above the 95th centile and a low diastolic blood pressure fell below the 50th centile. Reference: Appendix 5.

Table 2 above shows there were statistically significant differences in the mean systolic blood pressure, mean temperature and in the proportion of infants with a temperature greater than 38.5 °C, on comparison of cases with isonatremic infants. Systolic blood pressures below the 50th centile or diastolic blood pressures above the 95th centile were not detected in both groups.

Table 3: Comparison of clinical parameters between cases and hyponatremic controls.

Variable	Cases		Hyponatremic		O.R	95% C.I	p value
	Mean	S.D	Mean	S.D			
Age (months)	6.6	±3.3	6.7	±3.7	1.0	0.9 – 1.1	0.81
Length for age (Cm) mean z score, S.D	-0.28	± 0.89	- 0.12	± 0.74	0.6	0.5 – 1.0	0.75
Temperature (°C):							
Mean S.D	38.5	± 4.2	38.0	± 1.2	1.9	1.3 – 2.7	<0.001*
> 38.5°C (no. %)	39	70.9	20	36.4	4.2	1.8 – 6.8	0.02*
Respiratory rate: (cycles per minute)	55.0	±16.0	48.0	± 14.0	1.0	0.9 – 1.05	0.06
Systolic blood Pressure (mmHg):							
Mean S.D	99.7	±4.7	93.5	±7.4	1.2	1.1 – 1.2	<0.001*
High# (No. %)	6	10.6	5	9.0	1.0	0.8 – 1.3	0.82
Diastolic blood Pressure (mmHg):							
Mean, S.D	59.4	± 5.2	57.3	± 7.3	1.0	0.9 – 1.1	0.26
Low# (No. %)	2	3.6	6	10.9	0.3	0.2 – 1.4	0.27
Pulse rate: mean, S.D (beats per min.)	123.3	± 19.8	112.9	± 24.9	1.1	1.09 – 1.2	0. 02*
Glasgow coma scale Mean, S.D	9	± 2.4	10	± 2.3	11.0	0.9 – 1.2	0.96

*Statistically significant

A high systolic blood pressure fell above the 95th centile and a low diastolic blood pressure fell below the 50th centile. Reference: Appendix 5.

As shown in table 3 above there were statistically significant differences in the mean systolic blood pressure, mean pulse rate, mean temperature and in the proportion of infants with a temperature greater than 38.5 ^{o}C, when cases were compared to hyponatremic infants. Systolic blood pressures below the 50^{th} centile or diastolic blood pressures above the 95^{th} centile were not detected in both groups.

II. PRESENTING COMPLAINTS.

Table 4: Comparison of presenting complaints between cases and isonatremic controls.

Presenting Complaint	**Cases** (n = 55)	**Isonatremic** (n = 55)	**O.R 95% C.I**	**p value**
Diarrhea:				
no. %	30 54.5	37 67.2	0.6 0.4 – 1.1	0.08
Mean duration (days), S.D	2.5 ± 3.4	3.7 ± 4.2	0.9 0.8 – 1.0	0.12
Mean Motions per day S.D	3.0 ± 3.4	3.6 ± 3.4	0.9 0.8 – 1.0	0.44
Vomiting:				
no. %	47 85.5	49 89.0	0.7 0.6 – 1.1	0.28
Mean bouts/day, S.D	8.5 ±4.4	4.5 ± 3.5	1.3 1.1 – 1.4	<0.001*
Mean duration (days), S.D	4.5 ±4.1	3.7 ±4.8	1.0 0.9 – 1.1	0.38
> 8 times /day: no. %	40 72.7	12 21.8	9.5 2.3 – 15.1	<0.001*
Vomiting Everything: no. %	25 45.5	7 12.7	9.1 3.6 – 24.7	<0.001*
Refusal to feed: no. %	48 87.2	37 67.2	3.3 1.3 – 8.8	0.01*
Fever:				
no. %	37 67.3	33 60.0	1.3 1.0 – 1.9	0.25
Mean duration, S.D	5.0 ±5.2	4.6 ±8.7	1.0 0.9 - 11	0.77
Convulsions no. %	22 40.0	14 25.4	1.7 0.8 – 4.3	0.10
Excessive Sleepiness no. %	29 52.7	17 30.9	2.5 1.1 – 5.4	0.02*

*Statistically significant

As indicated in Table 4 above, cases were significantly more likely to present with complaints of vomiting everything, refusal to feed, and excessive sleepiness compared to isonatremic controls. In addition, a statistically significant difference was observed between cases and isonatremic controls on comparison of the mean vomiting bouts per day and in the proportions of infants who vomited more than eight times in a day.

Table 5: Comparison of presenting complaints between cases and hyponatremic controls.

Presenting complaint	**Cases** (n = 55)		**Hyponatremic** (n = 55)		**O.R**	**95% C.I**	**p value**
Diarrhea							
No. %	30	54.5	42	76.4	0.37	0.2 – 0.9	0.03*
Mean duration (days), S.D	2.5	± 3.4	5.7	6.9	0.9	0.8 – 1.0	<0.001*
Mean Motions /day, S.D	3.0	± 3.4	4.4	3.7	0.9	0.8 – 1.0	0.06
Vomiting							
no. %	47	85.5	40	72.7	2.2	0.8 – 5.6	0.15
Mean duration (days), S.D	4.5	± 4.1	3.0	3.3	1.1	0.9 – 1.2	0.05
Mean bouts/day, S.D	8.5	± 4.4	3.8	3.6	1.2	1.1 – 1.5	<0.001*
> 8 times /day: (no. %)	40	72.7	10	18.2	12	3.3 – 20.1	<0.001*
Vomiting Everything: no. %	25	45.5	7	12.7	7.6	3.0 – 19.8	<0.001*
Refusal to feed: no. %	48	87.2	42	76.4	2.1	0.8 – 5.8	0.14
Fever							
No. %	37	67.3	35	63.4	1.1	0.5 – 2.3	0.80
Mean duration, S.D	5.0	± 5.2	4.6	3.5	1.0	0.9 – 1.2	0.25
Convulsions: no. %	22	40.0	17	30.9	1.5	0.7 – 3.3	0.32
Excessive Sleepiness: no. %	29	52.7	26	47.3	1.2	0.6 – 2.4	0.70

*Statistically significant

Table 5 above shows that a complaint of diarrhea was significantly unlikely to be observed among the cases as compared to hyponatremic controls. Cases had a significantly shorter duration of diarrhea and higher frequency of vomiting bouts in a day as compared to hyponatremic controls. Cases were also significantly more likely to present with a complaint of vomiting everything. A significantly larger proportion of cases vomited more than eight times in a day compared to hyponatremic controls.

III. PRESUMPTIVE DIAGNOSIS.

The presumptive diagnosis was made by the attending clinician and was recorded as the main illness or illnesses for which the infant presented at PFC for care.
Cases were twice as likely to have meningitis and five times more likely to have cerebral palsy compared to isonatremic controls. However, these differences were not statistically significant, as shown in Table 6 below.

Table 6: Comparison of frequency of presumptive diagnoses between cases and isonatremic controls.

Diagnosis	**Cases** (n = 55)		**Isonatremic** (n = 55)		**O.R**	**95% C.I**	**p value**
	No.	**%**	**No.**	**%**			
Pneumonia	25	45.5	29	52.7	0.75	0.3 – 1.5	0.45
Gastroenteritis	15	27.3	18	32.7	0.77	0.3 – 1.7	0.53
Meningitis	11	20.0	6	10.9	2.0	0.6 – 6.8	0.18
Malnutrition	4	7.2	3	5.5	1.35	0.8 – 2.8	0.75
Cerebral palsy	5	9.0	1	1.8	5.4	0.6 – 47.2	0.80
Total*	60		57				

*In the table above the number of diagnoses exceeds the number in each group due to occurrence of co-morbidity.

Table 7 below shows there were no statistically significant differences detected in the frequencies of the presumptive diagnoses recorded when cases were compared to hyponatremic controls. Among hyponatremic controls, no infant had a diagnosis of cerebral palsy.

Table 7: Comparison of frequency of presumptive diagnoses between cases and hyponatremic controls.

Diagnosis	Cases (n = 55)		Hyponatremic (n = 55)		O.R	95% C.I	p value
	No.	%	No.	%			
Pneumonia	25	45.5	29	52.7	0.75	0.3 – 1.5	0.50
Gastroenteritis	15	27.3	12	21.8	1.1	0.5 – 2.5	0.80
Meningitis	11	20.0	8	14.5	1.5	0.5 – 4.5	0.45
Malnutrition	4	7.2	6	10.9	0.45	0.1 – 1.4	0.16
Total*	60		51				

*In the table above the number of diagnoses exceeds the number in each group due to occurrence of co-morbidity.

IV. CHARACTERISTICS OF PRIMARY CARETAKERS.

Primary caretakers accompanied all the infants recruited into the study, and these were usually also the legal guardians. The age range for the primary caretakers of the cases was 16 to 33 years, while that of the isonatremic controls was 16 years to 43 years. The age range for the primary caretakers of hyponatremic controls was 16 to 50 years.

The mean age of the primary caretakers of cases was 23.09 (S.D ± 2.87) years while that of the isonatremic controls was 24.98 (S.D ± 2.64) years. This age difference was not statistically significant and was not associated with hypernatremia (O.R 0.9, 95% C.I 0.8 – 1.1, p value = 0.45). The mean age of the primary caretakers of hyponatremic controls was 23.6 (S.D ± 2.2) years. The age difference between primary caretakers of cases and that of hyponatremic controls was not statistically significant and was not associated with hypernatremia (O.R 0.9, 95% C.I 0.8 – 1.1, p value = 0.45).

Among the primary caretakers of hypernatremic infants, 6 (10.9%) of them had not undergone formal schooling. A similar observation was made among 4 (7.2%) of the primary caretakers of isonatremic controls and 5 (9.0%) of the primary caretakers of hyponatremic controls. However these differences were not statistically significant and absence of formal schooling was not a risk factor for hypernatremia (O.R 1.0, 95% C.I, 0.9 – 1.2, p value = 0.42 and O.R 1.0, 95% C.I, 0.8 – 1.2, p value = 0.44 for isonatremic and hyoponatremic controls respectively).

V. PRIMARY CARETAKERS' INTERVENTIONS.

Primary caretakers of hypernatremic infants were significantly less likely to have administered plain water compared to the primary caretakers of isonatremic infants, but significantly more likely to have administered ORS. Though not statistically significant, primary caretakers of cases were three times more likely to have administered herbs and withheld feeds compared to those of hyponatremic infants. These findings are presented in Table 8 below.

Table 8: Comparison of primary caretaker's interventions between cases and isonatremic controls.

Intervention	**Cases** (n = 55)		**Isonatremic** (n = 55)		**O.R**	**95% C.I**	**p value**
	No.	**%**	**No.**	**%**			
Withheld feeds	6	10.9	2	3.6	3.2	0.6 –16.8	0.13
ORS	29	52.7	16	29.0	2.7	1.2 – 5.9	<0.001*
SSS	20	36.4	18	32.7	1.2	0.5 – 2.6	0.68
Herbs	11	20.0	4	7.2	3.2	0.9 – 10.7	0.05
Food based liquids	39	70.9	43	78.2	0.9	0.3 – 2.0	0.83
Cow's milk	20	36.4	23	41.8	0.9	0.7 – 1.9	0.84
Formula	5	9.1	7	12.7	0.6	0.4 – 1.9	0.54
Previous health unit visit.	42	76.4	33	60.0	1.9	0.8 – 4.4	0.10
Plain water use	11	20.0	20	36.4	0.4	0.1 – 0.6	<0.001*

*Statistically significant

As shown in table 9 below, cases were significantly less likely to have received plain water compared to hyponatremic infants. There were no statistically significant differences observed for other interventions.

Table 9: Comparison of primary caretakers' interventions between cases and hyponatremic controls.

Intervention	Cases (n = 55)		Hyponatremic (n = 55)		O.R	95% C. I	p value
	No.	%	No.	%			
Withheld feeds	6	10.9	4	7.2	1.56	0.6 – 5.8	0.50
ORS	34	61.8	25	45.5	1.3	0.6 – 2.9	0.45
SSS	20	36.4	24	43.6	1.2	0.5 – 2.6	0.68
Herbs	11	20.0	8	14.5	1.5	0.5 – 3.9	0.45
Food based liquids	39	70.9	38	69.0	1.0	0.7 –8.6	0.13
Cow's milk	29	52.7	31	56.3	0.9	0.4 – 1.9	0.8
Formula	5	9.1	4	7.2	1.2	0.6 – 2.1	0.34
Previous health unit visit.	42	76.4	39	70.9	1.9	0.8 – 4.3	0.10
Plain water use	11	20.0	30	54.5	0.2	0.1 – 0.5	<0.001*

*Statistically significant

RESULTS OF MULTIVARIATE ANALYSIS OF RISK FACTORS FOR HYPERNATREMIA

Table 10: Multivariate analysis of risk factors for hypernatremia- comparison of cases and isonatremic controls.

Risk factor	Cases		Isonatremic		Adjusted O.R	95% C.I	p value
Rectal temperature							
> 38.5^{0}C: no. %	39	70.9	22	40	2.4	1.5 – 3.8	<0.001*
mean, S.D	38.5	±4.2	38.0	±4.2	3.2	1.7 – 5.8	<0.001*
Vomiting > 8 times in 24 hrs: no. %	40	72.7	12	21.8	12.8	4.04 - 40.8	<0.001*
Vomiting bouts / day Mean, S.D	8.5	±4.4	4.5	±3.5	0.8	0.6 – 1.1	0.13
Vomiting everything no. %	25	45.5	7	12.7	15.4	4.4 – 54.2	<0.001*
Excessive sleepiness no. %	29	52.7	17	30.9	4.5	1.5 – 13.4	0.005*
Cerebral palsy: no. %	5	9.0	1	1.8	6.5	0.5 – 90.2	0.15
Refusal to feed : no. %	48	87.2	37	67.2	1.1	0.25 - 4.9	0.89
ORS use: no. %	29	52.7	16	29.0	2.2	0.75 – 6.5	0.15
Herbs : no. %	11	20.0	4	7.2	2.2	0.41 – 11.8	0.35
Systolic blood Pressure: mean, S.D	99.7	± 4.7	94.1	±6.0	0.98	0.88 – 1.09	0.79
Pulse rate: mean, S.D	123	±19.8	120	±20.0	0.98	0.95 – 1.01	0.41
Plain water: no %	11	20.0	20	36.4	0.2	0.1 – 0.6	0.01*

*Statistically significant

Table 10 above shows the results of multivariate analysis done for significant risk factors for hypernatremia detected on univariate analysis that compared cases and isonatremic controls. Significant risk factors for hypernatremia include vomiting more than eight times within 24 hours, vomiting everything, a rectal temperature of at least 38.5^0C, and excessive sleepiness. Use of plain water was significantly unlikely to be associated with hypernatremia.

Table 11: Multivariate analysis of risk factors for hypernatremia-comparison of cases and hyponatremic controls.

Risk factor	Cases		Hyponatremic		Adjusted O.R	95% C.I	p value
Rectal temperature:							
> 38.5^0C: no. %	39	70.9	20	36.4	2.4	1.6 – 3.7	<0.001*
mean, S.D	38.5	±4.2	38.0	±1.2	1.00	0.9– 1.2	0.89
Vomiting > 8 times in 24 hrs: no. %	40	72.7	10	18.2	16.98	5.3– 54.2	<0.001*
Vomiting:							
bouts / day, mean, S.D	8.5	±4.4	3.9	± 3.6	0.69	0.5 – 6.8	0.75
duration days, mean S.D	4.5	±4.1	3.0	±3.3	1.1	0.9 – 1.4	0.24
Vomiting everything no. %	25	45.5	7	12.7	2.1	0.3– 12.0	0.39
Diarrhea duration (days) mean, S.D	2.5	±3.4	5.7	±6.9	0.8	0.7 – 0.9	0.03*
Systolic blood Pressure: mean, S.D	99.7	± 4.7	93.5	±7.4	1.2	0.8 – 1.4	0.06
Pulse rate: mean, S.D	123	±19.8	112.9	±24.9	1.0	0.8 – 1.0	0.6
Plain water: no %	11	20.0	30	54.5	0.26	0.1 – 0.5	0.008*

*Statistically significant

Table 11 above shows the results of multivariate analysis of significant risk factors detected on univariate analysis that compared cases and hyponatremic controls. Vomiting more than eight times a day and a rectal temperature greater than 38.5^0C were significant risk factors for hypernatremia. Use of plain water and a diarrheal duration exceeding two days were significantly unlikely to be associated with hypernatremia.

CLINICAL OUTCOMES

Table 12: Comparison of adverse clinical outcomes between cases and isonatremic controls.

Adverse Outcome	Cases (n = 55)		Isonatremic (n = 55)		O.R	95% C. I	p value
	No.	%	No.	%			
Death	19	34.5	12	21.8	1.8	0.8 - 4.4	0.14
Convulsions	5	9.0	5	9.0	1.0	0.3 - 3.6	1.00
Hypertonia	3	5.5	1	1.8	3.1	0.1 - 30.9	0.29
Altered consciousness	12	21.8	5	9.0	2.7	0.9 - 8.5	0.06
Overall	*39*	*72.7*	*23*	*41.8*	*3.3*	*1.1 – 8.1*	*0.05**

*Statistically significant

As presented in Table 12 above, adverse clinical outcomes were three times more likely to be observed among cases than among isonatremic controls. This difference was statistically significant.

Cases were three times more likely to develop hypertonia and two times more likely to have an altered level of consciousness compared to isonatremic controls. These findings were not statistically significant. The difference in the mortality rates between cases and isonatremic controls was also not statistically significant.

Table 13: Comparison of adverse outcomes between cases and hyponatremic controls.

Adverse Outcome	Cases (n = 55)		Hyponatremic (n = 55)		O.R	95% C.I	p value
	No.	%	No.	%			
Death	19	34.5	18	32.7	1.0	0.5 – 3.0	0.41
Convulsions	5	9.0	3	7.3	1.7	0.3 – 7.6	0.20
Altered consciousness	12	21.8	6	10.0	2.2	0.5 – 6.1	0.18
Overall	*36*	*70.9*	*27*	*49.0*	*2.5*	*0.99 – 5.1*	*0.06*

Table 13 above shows that though the differences observed in the frequencies of adverse clinical outcomes on comparison of cases and hyponatremic controls were not statistically significant, cases were two and a half times more likely to have an adverse clinical outcome and were twice as likely to have an altered level of consciousness as compared to hyponatremic controls.

Hypertonia was not observed in any of the hyponatremic controls during follow up. In addition, a comparison of GCS rating between cases and both controls with altered consciousness during follow up did not reveal statistically significant differences. (O.R 1.1 95%C.I 0.9 – 1.4, p value = 0.38 and O.R 1.0 95% C.I 0.9 – 1.2, p value = 0.91 respectively)

Among hypernatremic infants 57.9% (11 out of 19)) died within 24 hours of admission as compared to 25% of isonatremic controls (3 out of 12) over the same duration. This difference was statistically significant (O.R 4.1 95% C.I 1.1 – 14.8, p value = 0.05).

Among hyponatremic controls 44% (8 out of 18) died within 24 hours of admission. The difference in proportions of 24-hour mortality between cases and hyponatremic controls not was statistically significant (O.R 1.7, 95% C.I 0.8 – 3.5, p value = 0.1).

Figure 2 below compares the probability of survival of cases with that of isonatremic controls. The probability survival for cases declined significantly at two days of the hospital stay. However isonatremic infants did not have a significantly better probability of survival as the log rank test for difference between the two groups had chi square = 1.3, p value = 0.263.

Fig. 2: Comparison of probability of survival between cases and isonatremic controls.

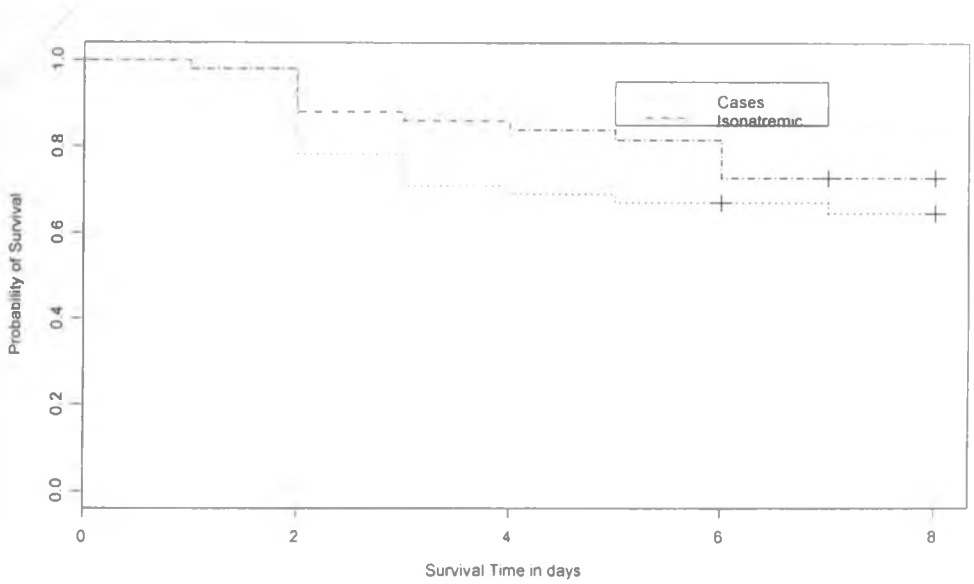
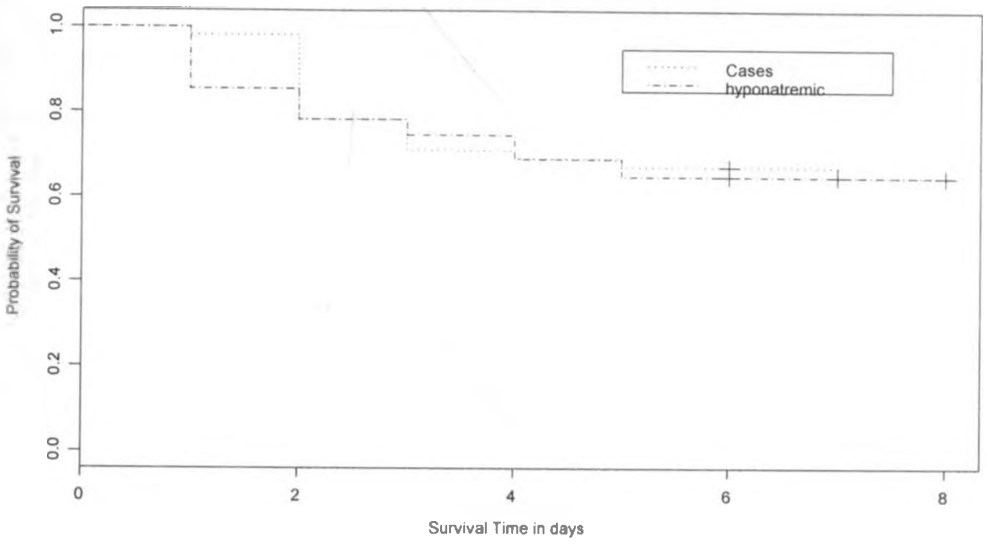


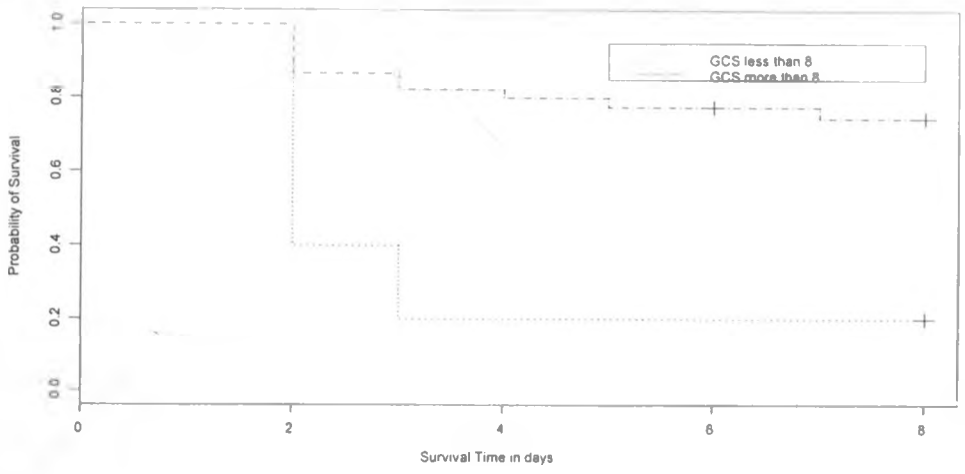
Fig. 3: Comparison of probability of survival between cases and hyponatremic controls.



From figure 3 above there seems to be no difference between the two curves. The probability of survival with time in the two groups interacts. The log rank test for difference between the cases and the hyponatremic controls had a Chi square = 0.3, p= 0.599. Hence, there was no statistically significant difference in survival between cases and hyponatremic controls.

Figures 4, 5 and 6 below indicate how the probability of survival varied in each of the study groups in relation to a Glasgow coma scale rating less than or greater than eight on presentation.

Fig 4. Comparison of probability of survival for hypernatremic infants with a Glasgow coma scale rating greater than eight, compared to those with a rating less than eight at presentation.



As shown in figure 4 above, a significant decline in the probability of survival with time is observed in hypernatremic infants with a GCS rating less than eight. The log rank test for difference between those with a GCS greater than eight and those with one below eight had a Chi square = 15.8, p value <0.001. Hence there was a statistically significant difference between the two groups in the probability of survival with time.

Fig 5. Comparison of probability of survival for isonatremic infants with a Glasgow coma scale rating greater than eight, compared to those with a rating less than eight at presentation.

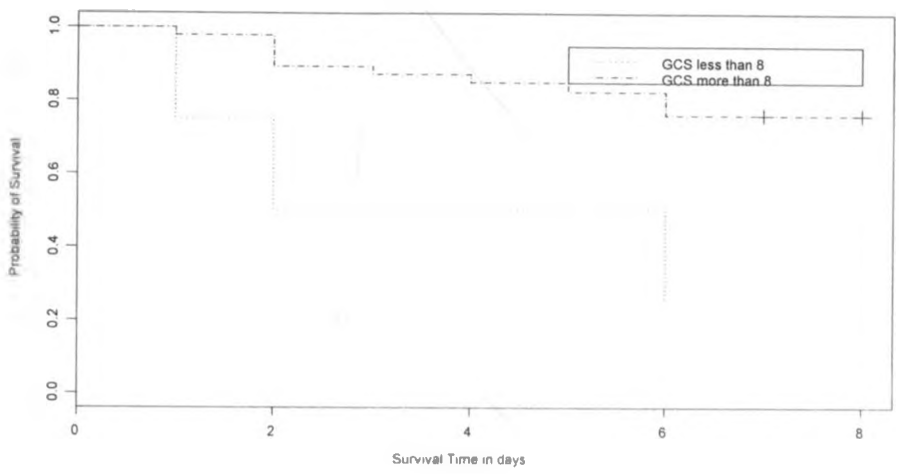
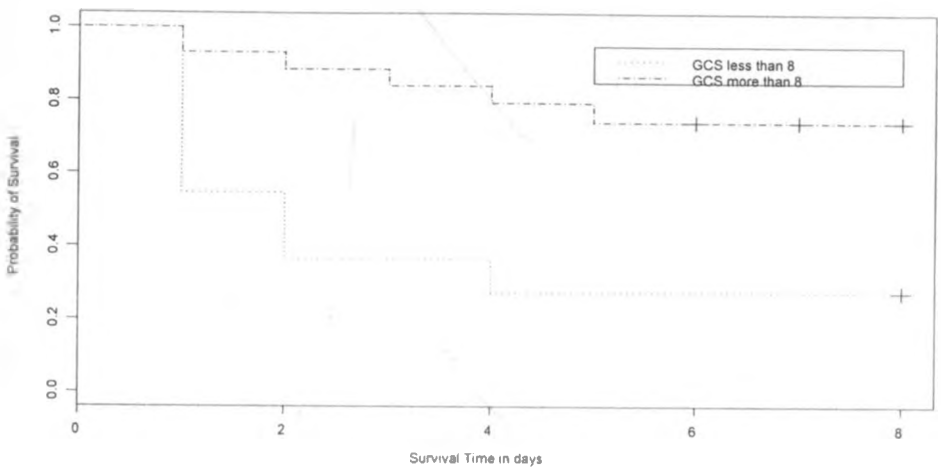


Figure 5 above shows a significant decline in the probability of survival for isonatremic infants with a GCS rating less than eight at six days after admission. The log rank test for difference between isonatremic infants with a GCS greater than eight and those with one below eight has a Chi square = 6.5, p value =0.01. Hence there was a statistically significant difference between the two groups, in the probability of survival for isonatremic infants with time.

Fig 6. Comparison of probability of survival for hyponatremic infants with a Glasgow coma scale rating greater than eight, compared to those with a rating less than eight at presentation.



As presented in figure 6 above, there was a significant difference in the probability of survival for hyponatremic infants who who had a GCS below eight as compared with those with a GCS above eight on presentation. The log rank test for difference between isonatremic infants with a GCS greater than eight and those with one below eight had a Chi square = 12.9, p value < 0.001.

DISCUSSION

Severe dehydration contributes significantly to mortality in children in the developing world, part of which can be attributed to hypernatremia. Guidelines provided by World Health Organization (WHO) for resource poor situations do not emphasize on the need for a serum sodium profile to enhance rehydration therapy (40). The importance of a serum sodium level as part of the basics of acute and emergency care in severely dehydrated infants especially in a referral center such as KNH before use of intravenous fluids cannot be over- emphasized. Where serum sodium derangements are detected, monitoring sodium levels during therapy every two to four hours as recommended should be adhered to in order to reduce morbidity and mortality (1).

The prevalence of hypernatremia in this study was 5.9%, which exceeds proportions reported in recent studies, which reported a declining prevalence over the last two decades (10, 25, 38). The higher prevalence observed in this study may be because only severely dehydrated infants were included. Infancy and severe dehydration are known risk factors for hypernatremia (2, 5, 35). Comparative studies included older children who could express thirst, and those with less severe degrees of dehydration (10, 25, 38). The mean age of the patients in Moritz's study was four years while that of patients in Wasunna's study was eleven months (25, 38). The higher prevalence observed was also due to inclusion of infants with other illnesses apart from, or in addition to diarrhea. Water losses are increased in such illnesses as pneumonia and meningitis due to multiple mechanisms including tachypnea, fever, and reduced fluid intake.

Fever with a rectal temperature of at least 38.5^{o}C was a significant risk factor for hypernatremia in this study. A rise in body temperature is associated with an increase in insensible water loss and an increase in the basal metabolic rate, which is accompanied by an increase in body water requirements (2, 5).

Higher water requirements in febrile infants were possibly not met in the presence of concurrent processes such as frequent vomiting which therefore predisposed those infants who had a higher rectal temperature to hypernatremia.

There was a significant difference between the mean systolic blood pressures of the cases and that of both controls. This can be explained by the relative preservation of the intravascular volume in those with hypernatremic dehydration as compared to those having non - hypernatremic dehydration (7, 9). Normal mean systolic and diastolic blood pressures were observed in this study population in spite of the severe dehydration. This may have been due to initiation of effective compensatory mechanisms such as tachycardia and peripheral vasoconstriction (49). Indeed the tachycardia observed among both cases and controls was partly in response to hypovolemia due to severe dehydration and served to maintain the infants' blood pressures within the normal range (49). The difference observed in the pulse rates between the cases and hyponatremic controls may have been occasioned by the higher mean temperature recorded among cases. An increase of one degree centigrade in body temperature has been associated with an increase in the heart rate by about ten beats per minute.

The infant gastrointestinal system is presented with a large volume of fluid estimated at 3000 milliliters each day. A third of this is in the form of ingested fluids while two thirds is from mucosal gastrointestinal secretions. The salivary glands and the stomach produce a third of the mucosal secretions. Fluid absorption in the gastrointestinal tract occurs mainly in the jejunum and ileum with only about 200 milliliters being lost in stool. Vomiting causes loss of ingested fluids and the upper gastrointestinal secretions (50). Recurrent vomiting would therefore, cause a large water deficit and is likely to have contributed to the high prevalence of hypernatremia observed (5, 51).

One of the signs of severe illness in infants according to integrated management of childhood illnesses (IMCI) guidelines is excessive vomiting which is referred to as "vomiting everything" (52). This complaint was significantly associated with hypernatremia as well as a vomiting more than eight times in a day, both of which are indicators of excessive vomiting which causes a significant water deficit.

Excessive sleepiness in a child would reduce oral fluid intake and explains why it was a risk factor for hypernatremia in this study population. A complaint of refusal to feed and withholding of feeds by primary caretakers were observed more frequently among hypernatremic infants. These events reduced water intake in this group of patients making them more likely to develop hypernatremia and also contributed to the higher prevalence of hypernatremia observed.

Diarrhea resulting from increased motility, secretory and osmotic mechanisms, causes loss of both sodium and water in stool (5, 50). This observation suggests that additional processes that prevented water intake or aggravated water losses predisposed cases to hypernatremia and not diarrhea in isolation. In this study, diarrhea was not a risk factor for hypernatremia and was significantly unlikely to be associated with hypernatremia. Gastroenteritis was the second most common diagnosis made in the study population, and occurred in only 27.3% of the hypernatremic infants. This observation contrasts that of previous studies that concluded gastroenteritis was the most common cause of hypernatremia (6, 30, 32 – 36). However, these studies excluded children having other conditions apart from gastroenteritis, who were included in this study. When all cases of hypernatremia are considered, a declining contribution of gastroenteritis has been noted in recent years (10, 53).

Tachypnea, fever, vomiting and refusal to feed were observed in those with pneumonia. These symptoms increased water losses, and predisposed infants with pneumonia to hypernatremic dehydration. Previous studies have shown that only half of the caretakers of infants with pneumonia recognize the need to provide fluids

to infants with fever and tachypnea hence placing these infants at a higher risk of significant dehydration. (54)

Though not statistically significant, cerebral palsy was five times more likely to occur among cases, compared to isonatremic controls. The infants recruited in this study had cerebral palsy as well as either pneumonia or gastroenteritis. Cerebral palsy is associated with feeding difficulties and reduced oral fluid intake due to poor co-ordination of the swallowing reflex. In these patients therefore, hypernatremic dehydration may have been due to prolonged reduction in water intake compounded by increased fluid losses. Hypernatremia has been associated with prior neurological impairments by Moritz, Finberg, and Listernick (10, 13, 55).

Oral rehydration salts (ORS) is recommendeded for the management of dehydration in children. (40) An increase in ORS use from 11% reported in 1988 to 45% in this study was observed (22). Previous studies have associated use of ORS with hypernatremic dehydration resulting from an inadvertent sodium overload in the children who consumed wrongly reconstituted ORS solutions. (30, 33) This association however was not observed in this study.

Homemade salt sugar solution use was not a risk factor for hypernatremia. Of note was the decline in homemade salt sugar solution use that was reported as 69% in 1988 while in this study it was 37.5% (22). Given the difficulties of precise measurements of salt and sugar to make rehydration solutions, and the wide availability of ORS, use of homemade salt sugar solutions should be discouraged.
Herbal medicine use was reported by more primary caretakers of hypernatremic children compared to those of non-hypernatremic infants. Though this finding was not statistically significant, hypernatremia is a recognized complication of herbal medicine use and is caused by the addition of sodium bicarbonate to herbal preparations (58, 59).

Administration of plain water to the infants in this study population was significantly unlikely to be associated with hypernatremia as this intervention reduced the water deficit making hypernatremia less likely.

Whereas previous studies have linked a primary caretaker's interventions to their age and level of education these associations were not demonstrated in this study. This was probably due to an increase in public awareness of appropriate interventions, which would not be influenced by these two factors (22, 23).

Known complications of hypernatremic dehydration include death, hypertonia, convulsions, hemiplegia and residual brain deficits. Survivors of hypernatremic dehydration have a 15 times higher risk of neurological sequelae compared to those who survive isonatremic dehydration. The occurrence of complications has been associated with inappropriate or absence of intervention (1–8). Inappropriate management of cases of hypernatremia may occur where a serum sodium level is not determined prior to start of management.

The mortality rate among the hypernatremic infants was 34.5% which was more than twice that reported by Pevalesky and Moritz at 16% (9, 10). This mortality rate also greatly exceeded the average rate of 12% observed for all other children in the general pediatric wards of KNH during the study period (27). Mortality rate among the cases did not differ significantly from that observed in both control groups. The higher mortality rate and lack of a difference between cases and controls may have been due to the fact that all the infants in the study population were severely dehydrated with associated severe illnesses and therefore were already at a greater risk of death as compared to others in the general pediatric wards.

A higher 24-hour mortality rate was observed among cases compared to both controls. Wrong choice and flow rate of rehydration fluids could have contributed to this occurrence. Correction of hypernatremia requires lowering of the sodium level

and correction of the fluid deficit over a period of about 48 hours. Decrease in sodium levels should occur at a rate not exceeding half to one mmol/l per hour (1). Early mortality could also have resulted from intracranial hemorrhage, a known complication of acute severe hypernatremia.

Neurological complications were observed in 20 (36.4%) of the hypernatremic infants. These complications included seizures, hypertonia and altered level of consciousness. In Moritz's and Ayus' study, only 10 (15%) of hypernatremic children in that study developed similar complications (10). The high rate of complications observed in this study could be due to delays in institution of appropriate management, given that 76% of the cases had visited other health facilities at least once before coming to KNH. A serum electrolyte profile was not done in the peripheral health units.

Hypertonia was three times more likely to be observed among cases as compared to isonatremic controls. Moritz and Ayus reported hypertonia in two of ten hypernatremic infants with neurological complications (10). Though cases and both controls appeared to have no difference in the likelihood of developing convulsions, among hypernatremic children convulsions are associated with cerebral edema that results from rapid lowering of serum sodium levels during rehydration. Cerebral edema is also associated with alteration of the level of consciousness and death due to resultant brain stem herniation.

On the modified Glasgow coma scale used in pediatrics, a coma scale rating below eight signifies deep coma (47). The observation of a significant decline in the proportions of infants surviving with a GCS rating less than eight at presentation in the three study groups, may be due to the possibility that these infants did not receive attention commensurate to their degree of illness.

Though other potentially life-threatening derangements such as hypoglycemia, hypokalemia and hyperkalemia could have contributed to the observed adverse outcomes, it was not possible to exclude them in this study due to financial constraints. A post-rehydration weight was not taken, and this precluded a weight for length analysis for detection of acute malnutrition as the pre-rehydration weight was confounded by varying degrees of weight loss in each of the infants in the study population.

CONCLUSIONS

- The prevalence of hypernatremia among severely dehydrated infants at Kenyatta National Hospital is 5.9%.

- Excessive vomiting, a rectal temperature equal to or greater than 38.5^0C and excessive sleepiness are significant risk factors for hypernatremia.

- Severely dehydrated infants with hypernatremic dehydration are more likely to have an adverse clinical outcome compared to those without hypernatremia. Infants with hypernatremic dehydration have higher early mortality compared to those with isonatremic dehydration. In addition, severely dehydrated infants who present in deep coma are more likely to die than those who do not irrespective of serum sodium level.

- Presence of diarrhea and prior administration of plain water to severely dehydrated infants are associated with a significantly reduced risk of hypernatremia.

RECOMMENDATION

- Severely dehydrated infants who have excessive vomiting, excessive sleepiness, or a rectal temperature greater than 38.5^0C, should be considered at a high risk of having hypernatremia and should thus be prioritized for determination of serum sodium level.

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APPENDIX 1(40)

W.H.O GUIDELINES ON CLASSIFICATION OF DEHYDRATION.

Condition	Well, alert	Restless	Lethargic or unconscious
Eyes Thirst	Normal Absent	Sunken thirsty	Sunken Drinks poorly OR unable to drink.
Skin pinch	Normal	Slow recoil	Very slow recoil
Decide	No signs of dehydration	Some Dehydration	SEVERE DEHYDRATION
Treat	Plan A	Plan B	Plan C urgently

Source: The Treatment of diarrhea. A manual for physicians and other senior health workers. WHO/CAH/03.7, 10/03

APPENDIX 2

GUARDIAN'S CONSENT FORM FOR PARTICIPATION IN THE STUDY

Participants serial number_____ Date_____

Child's name_____

Study title: Prevalence and risk factors for hypernatremia in severely dehydrated infants at Kenyatta National Hospital.

Investigator: Dr. Pauline Samia, postgraduate student, university of Nairobi.
Emergency contact. Tel number 0722871067

Supervisors:
Dr. G. Irimu, Lecturer, Department of Paediatrics and Child Health, University of Nairobi.
Prof. W. Macharia, Associate professor, Department of Paediatrics and Child Health, University of Nairobi.
Dr. A. Amayo, Senior Lecturer, Department of Human Pathology, University of Nairobi.

Investigator's statement.
We are requesting you and your baby to participate in a research study. The purpose of this consent form is to give you information you will need to help you decide whether to participate in the study.

Introduction
Some infants who are seen at the pediatric filter clinic at Kenyatta National Hospital have loss of water in their bodies due to various illnesses. They sometimes also develop abnormalities in the blood sodium (salt) levels, which would require special attention in order to correct it.
This study seeks to find out what factors put children less than one year of age at risk for high sodium levels in blood when they are dehydrated

Benefits of the study
The results of the blood test done on your baby will be given to your doctor for use in the treatment of your baby. The results obtained from this study will help in the management of other children suffering from similar ailments.

The risks

Drawing blood may be a little bit uncomfortable for your baby but all precautions will be taken to avoid any complications.

Confidentiality

All the information obtained will be held in confidence. We will not publish or discuss in public anything that could identify you or your baby. You are free to withdraw from the study if you so wish.

Do you have any questions? Yes ☐ No. ☐
Do you agree to participate? Yes ☐ No ☐

_____ _____

Investigator's signature Investigator's name

Date_____

Subject statement (guardian)

I, Mr. / Mrs. /Ms _____ am the legal guardian/

parent of _____, and I give consent for my child to participate in the study on: "Prevalence and risk factors for hypernatremia in severely dehydrated infants at Kenyatta National Hospital." I have had a chance to ask questions about the research to which satisfactory answers have been given. I understand I can withdraw from the study without any penalty.

_____ _____

Guardian's signature Date

Cc Subjects' file
Investigator's file.

APPENDIX 3

DATA COLLECTION SHEET.

Serial no.
Date. Name.

A. VITAL SIGNS

01 AGE (months)
02 SEX
03 weight kg
04 length cm
05 BP / mmHg
06 Temp. °c
07 Resp. Rate /min
08 Pulse rate /min

B. Level of consciousness (GCS) /15

C. COMPLAINTS.

01.Diarrhoea	:011 duration (days)	: 012 motions / 24 hrs
02.Vomiting	:021 duration (days)	: 022 bouts/ 24hrs.
03. Vomits everything	: 031present	:032 absent
04. Hotness of body	: 041 duration (days)	: 042 absent
05. Convulsions	:051 present	:052. absent
06. Excessive sleepiness:	:061 present	:062 absent
07. Refusal to feed	: 071 present	:072 absent

D. PRIMARY CARETAKER'S INTERVENTIONS

01. Withheld feeds	011. YES	012. NO
02. ORS	021.YES	022. NO.
03. Home made salt and sugar solution	031. YES	032. NO
04. Herbal medicine	041. YES	042. NO
05. Food based liquids	051. YES	052. NO
06.cows milk	061.YES	062.NO
07. formula milk (specify)	071. YES	072 NO
08. Health unit visit	081YES	082. NO
09. Plain water.	090: YES	091:NO

010 Guardian's age

011 Guardian's level of education 111. None 112.Primary (specify class)

113.Secondary and above

E. PRESUMPTIVE DIAGNOSIS

01 Meningitis 02.Gastroenteritis

03. Pneumonia 04.Others (specify)

G. Serum sodium level mmol/l

F.CLINICAL OUTCOME

01 Uneventful recovery

02. Altered consciousness GCS /15

03. Convulsions

04. Neurological impairment. (specify)

05. Death

APPENDIX 4

MODIFIED GLASGOW COMA SCALE (47)

Eye opening

4.Spontaneous

3.To speech

2.To pain

1. No opening

Best verbal response

5. Smile, interact

4. Crying, consolable

3. Inconsistently consolable

2. Grunts or moans

1. No response

Best motor response

6. Normal responsive movements

5. Withdraws to touch

4. Withdraws from pain

3.Flexion to pain- decorticate posturing

2. Extension to pain – decerebrate posturing

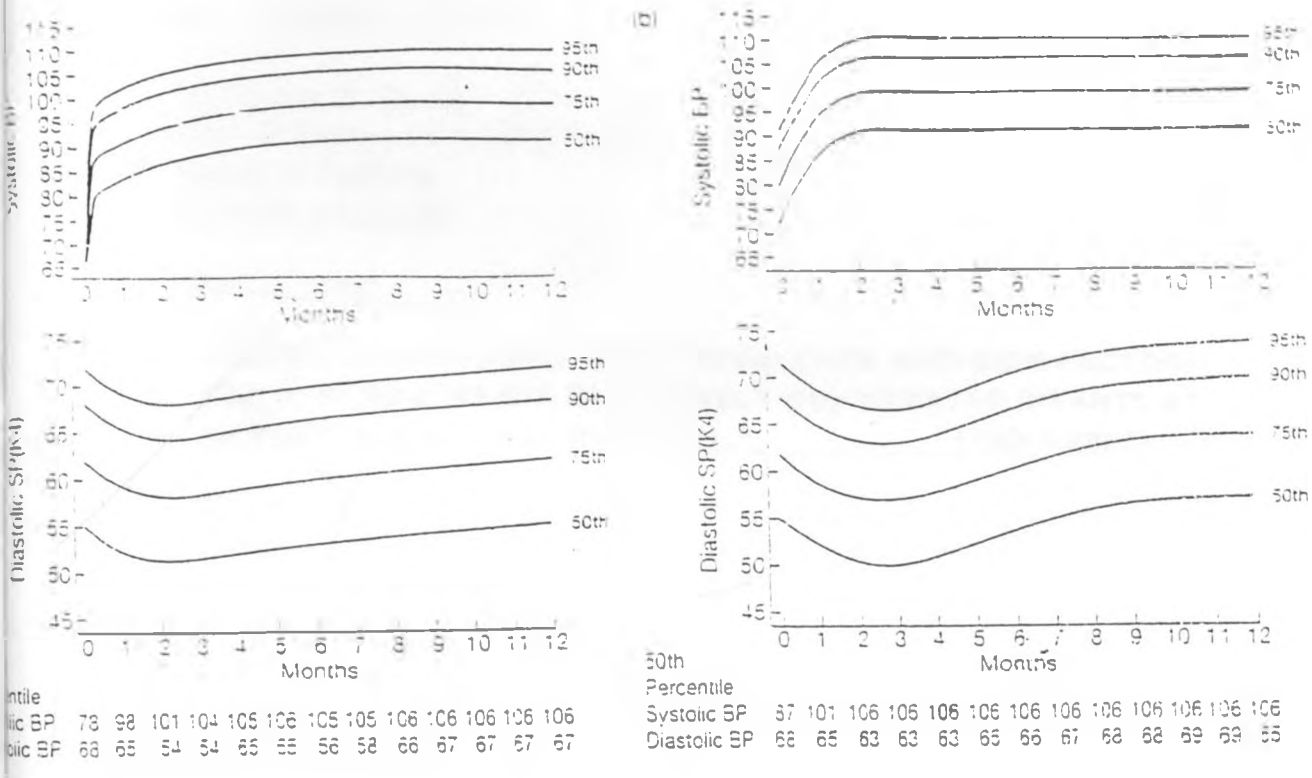
1. No response

APPENDIX 5

PEDIATRIC BLOOD PRESSURE MEASUREMENT REFERENCE CHARTS. (48)

a)Girls

b)Boys



Source: National Heart, Lung, and Blood pressure Institute. Report of the second task force on blood pressure control in children. Pediatrics 1987; 79: 1 – 25.

APPENDIX 6

ETHICS COMMITTEE APPROVAL LETTER.

KENYATTA NATIONAL HOSPITAL
Hospital Rd. along, Ngong Rd.
P.O. Box 20723, Nairobi.

Tel: 726300-9
Fax: 725272
Telegrams: "MEDSUP", Nairobi.
Email: KNHplan@Ken.Healthnet.org

Ref: KNH-ERC/01/2736

Date: 8th June 2005

Dr. Pauline W. Samia
Dept. of Paediatrics & Child Health
Faculty of Medicine
University of Nairobi

Dear Dr. Samia

RESEARCH PROPOSAL: "THE PREVALENCE AND RISK FACTORS FOR HYPERNATREMIA IN SEVERELY DEHYDRATED INFANTS AT KENYATTA NATIONAL HOSPITAL." (P48/4/2005)

This is to inform you that Kenyatta National Hospital Ethics and Research Committee has reviewed and approved your above cited research proposal for the period 8th June 2005 to 7th June 2006. You will be required to request for a renewal of the approval if you intend to continue with the study beyond the deadline given.

On behalf of the Committee, I wish you fruitful research and look forward to receiving a summary of the research findings upon completion of the study.

This information will form part of database that will be consulted in future when processing related research study so as to minimize chances of study duplication.

Yours sincerely,

Prof. A. M. GUANTAI
SECRETARY – KNH-ERC

cc: Prof. K. M Bhatt, Chairperson, and KNH-ERC
The Deputy Director (C/S), KNH
The Dean, Faculty of Medicine, UON
The Chairman, Dept. of Paediatrics & Child Health, UON
The, HOD. Medical Records, KNH
Supervisors: Dr.Grace Irimu, Dept. of Paed. & Child Health, UON
Dr. W.M. Macharia, Dept. of Paed.&Child Health, UON
Dr. A. Amayo, Dept. of Clinical Chemistry, UON