SERUM ELECTROLYTES IN NEONATES WITH MODERATE AND SEVERE HYPOXIC ISCHAEMIC ENCEPHALOPATHY ON THERAPEUTIC HYPOTHERMIA AT KENYATTA NATIONAL HOSPITAL

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H58/37283/2020
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A RESEARCH DISSERTATION SUBMITTED TO THE SCHOOL OF MEDICINE IN PART FULFILLMENT OF THE REQUIREMENT FOR THE AWARD OF DEGREE OF MASTER OF MEDICINE IN PAEDIATRICS AND CHILD HEALTH, FACULTY OF HEALTH SCIENCES, UNIVERSITY OF NAIROBI.

2023

DECLARATION

This dissertation is my original work and, to my knowledge, has not been present for the award of a degree in any university or academic forum

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LIST OF ABBREVIATIONS

AMPA- Amino-3-hydroxy-5-methyl-4-isoxazole propionate

APGAR- Appearance, Pulse, Grimace, Activity, Respiration

ATP - Adenosine triphosphate

HIE- Hypoxic Ischaemic Encephalopathy

KNH- Kenyatta National Hospital

Meq/L- milli equivalent per litre

NBU- Newborn Unit

NMDA -N-Methyl-D-aspartate

PTH-Parathyroid Hormone

TH- Therapeutic Hypothermia

DEFINITION OF TERMS

Apgar Score: A quick test performed on a newborn immediately after birth. I Five criteria are used to evaluate the baby; appearance, pulse, grimace, activity and respiration. These are scored on a scale from zero to two and the values summed up. The score ranges from zero to ten. The child is assessed at 1, 5 and 10 minutes(1)

Term Newborn: Infant born at or after 37 completed weeks

Hypercalcemia-serum calcium > 12 mg/dL (>3 mmol/L)

Hyperkalemia-serum potassium concentration >6 mEq/L

Hypernatremia-serum sodium concentration ≥150 mEq/L

Hypocalcemia-serum Calcium ≤8 mg/dL (2 mmol/L)

Hypokalemia-serum potassium concentration <3 mEq/L

Hyponatremia-serum sodium concentration ≤ 128 mEq/L

ABSTRACT

Background

Hypoxic Ischaemic Encephalopathy (HIE) is a birth complication affecting full term infants. Globally, it contributes to significant morbidity and mortality in newborns. In the developed world, the incidence of HIE is estimated at 1-8 per 1000 live births as compared to 26 per 1,000 in the developing world. HIE contributes significantly to morbidity and mortality in infants less than 24 months of age with more than 40% dying or developing severe neurological deficits. Therapeutic hypothermia is the only current proven neuroprotective therapy for treatment of moderate and severe HIE. It is initiated within the first six hours of life and has three phases; induction, cooling and rewarming. Core body temperature is maintained for 72 hours at 33°C to 35°C. This study aims to establish the serum sodium, calcium and potassium levels in babies with moderate and severe HIE and to compare these electrolyte levels with babies with moderate to severe HIE not undergoing Therapeutic Hypothermia at KNH. The results will inform better monitoring and care of these babies. There is paucity of literature on electrolyte disturbances associated with Therapeutic Hypothermia and findings from this study will add to this information.

Objectives

To determine the effect of Therapeutic Hypothermia on sodium, calcium and potassium levels in neonates with moderate and severe HIE in Kenyatta National Hospital

Methods

A prospective cohort study was conducted on 74 neonates with moderate and severe HIE admitted to KNH NBU. The cases, chosen using consecutive sampling were 37 neonates with moderate and severe HIE admitted to the KNH Newborn unit (NBU) who received Therapeutic hypothermia while the controls were 37 age and degree of HIE matched term neonates who were not cooled due to the limited number of cooling devices available at KNH NBU. Participants were identified using a predetermined inclusion and exclusion criteria.
Informed consent was obtained. Serum electrolytes (sodium, calcium and potassium) were measured on day 1(baseline), day 2(Cooling phase) and day 4 (rewarming phase) of life.

Data Analysis

Data analysis was then done using R Software version 4.2.2.
Inferential analysis was done on the trend of the electrolytes across the cooling and rewarming phase using paired T test. Further analysis was done where day 1 ,2 and 4 Calcium, Potassium and Sodium values for both groups were analysed using the 2 sample T test for between group differences. The results were presented as summary statistics, tables and graphs.

Ethical Considerations

The investigator did not assign subjects into the respective groups. The subjects in the control group were infants who met the criteria for Therapeutic Hypothermia but did not receive the intervention due to the limited number of cooling devices available at KNH NBU.

Results

74 neonates were enrolled into the study with 37 receiving Therapeutic Hypothermia and 37 in the control group. In the group undergoing Therapeutic hypothermia, at baseline, the mean calcium level was 1.99mmol/L (SD 0.19), sodium 131.62mmol/L (SD 6.59) and potassium 5.72 mmol/L (SD 1.11)

In the cooling phase, there was a statistically significant increase in calcium, mean difference 0.16mmo/l ($p<0.0001$). For potassium, the mean difference was -1.09 mmol/L ($p < 0.0001$), indicating a statistically significant decrease. In contrast, the mean difference for sodium was 0.89 mmol/L, but the p-value was not significant ($p = 0.5$).

In the rewarming phase, the mean difference for calcium was 0.2 mmol/L ($p < 0.0001$), indicating a statistically significant increase. For potassium, the mean difference was -0.36 mmol/L ($p = 0.0113$), indicating a statistically significant decrease. The mean difference for sodium was 3.1 mmol/L ($p = 0.0008$), which was also statistically significant, indicating a substantial increase in sodium levels during the rewarming phase compared to the cooling phase.

Overall neonates undergoing therapeutic hypothermia had higher mean calcium and sodium levels with lower mean potassium levels from baseline during both cooling and rewarming phases, with more significant changes in the latter.

In the Therapeutic Hypothermia group, hypocalcemia (72.9%), hyperkalemia (48.6%) and hyponatremia (35.1%) were reported on day 1 of life. The incidence of hypocalcemia reduced from 72.9% before TH to 5.4% after TH, hyponatremia reduced from 35.1%% before TH to 0% after TH and hyperkalemia a reduced from 48.6% before TH to 2.7% after TH. In this study, Therapeutic hypothermia did not result in significant further derangements of sodium, calcium and potassium levels from baseline.

There was no significant difference in sodium and potassium levels in the TH group compared to the non-TH group. However, the incidence of hypocalcemia was higher in the non-TH group (29.7%) compared to the TH group (5.4%). Here the difference between the two groups was statistically significant with a p value of 0.0043 and an odds ratio of 0.15 (95% Confidence Interval 0.01 – 0.94).

Conclusions

At baseline, both the TH and no TH groups had deranged serum electrolytes (hyperkalemia, hyponatremia and hypocalcemia). This indicates that Perinatal asphyxia causes derangements in these electrolytes. Therapeutic Hypothermia was not found to have further adverse derangements in sodium, potassium and calcium levels from baseline and has been associated with lower incidence of hypocalcemia, hyperkalemia and hyponatremia

Recommendations

All infants with moderate and severe HIE should have serum electrolytes monitored whether on Therapeutic Hypothermia or not.

1. Introduction and Literature Review

Hypoxic Ischaemic Encephalopathy (HIE) is a birth complication that affects term neonates. Globally, Hypoxic-ischemic encephalopathy (HIE) contributes significantly to neonatal morbidity, and mortality in the world. In the developed world, the incidence of HIE is estimated at 1-8 per 1000 live births as compared to 26 per 1,000 in the developing world. (2)(3) HIE causes significant morbidity and mortality in affected infants with more than 40% dying or developing severe neurological deficits before 24 months of age. (4).

Perinatal asphyxia is one of the leading causes newborn of death at Kenyatta National Hospital(5) Currently, Therapeutic Hypothermia (TH) is the only available treatment for neonates with moderate and severe HIE that has been shown to improve neurological outcomes.(6) Therapeutic Hypothermia started within the first 6 hours of life for infants with moderate and severe HIE has been shown to have neuroprotective effects which persist into childhood.(7) The Kenya National Newborn Guideline for Hospitals (2018) recommend that serum electrolytes should be monitored daily especially during the first three days of life in all neonates with HIE (8)

1.2 Therapeutic Hypothermia and HIE

HIE is associated with changes at the cellular level. Hypoxia and ischaemia result in two phases of energy failure; primary energy failure, and secondary energy failure with a latent phase between the two phases. In the primary phase there is reduction in oxygen supply and blood flow with resultant anaerobic metabolism. Lactic acid accumulates, adenosine triphosphate (ATP) levels fall and the sodium (Na+)/potassium (K+) pump fails. Sodium and water accumulate in the cells

leading to cytotoxic oedema. The latent phase lasts between 6 to 24 hours. Reperfusion occurs and cerebral metabolism recovers transiently. This is the therapeutic window and neuroprotective interventions such as therapeutic hypothermia can be implemented to prevent irreversible neuronal damage. If no intervention is instituted secondary energy failure occurs. Influx of sodium into the cells causes membrane depolarization and release of excitatory neurotransmitters including glutamate NMDA, Kainate and AMPA. NMDA causes activation of calcium channels with calcium accumulating in the cells. Calcium causes release of lipases and proteases and this results in apoptosis(9) (10)(11–13)

Therapeutic Hypothermia is neuroprotective. It acts by reducing metabolic rate and energy depletion, decreasing release of excitatory transmitters, altering ion flux and reducing apoptosis. TH also reduces oedema and vascular permeability (14,15)

In 2013 a Cochrane review found that Therapeutic Hypothermia reduced morbidity and mortality in infants with moderate and severe HIE. There was a reduction in severe neurodevelopmental dysfunction in infants at 18 months who underwent TH for moderate and severe HIE at birth. It included 11 randomised control trials and a total of 1505 infants. (16)

Therapeutic hypothermia is instituted within the first 6 hours of life. The target rectal temperature of 33.5℃ with a range of 33℃ to 34℃ is maintained for 72 hours. This is followed by rewarming at a rate of 0.5℃ per hour to normal temperature of 36.5℃-37.0℃ within 8 hours. (17–19)

Therapeutic Hypothermia has been associated with adverse effects during the induction, maintenance and rewarming phase. These include bradycardia, thrombocytopenia, subcutaneous fat necrosis, leukopenia, severe persistent pulmonary hypertension, and electrolyte derangements such as hypokalemia and hypocalcemia. (16,20,21)

Therapeutic hypothermia is currently given to infants above 36 weeks gestation. In preterm infants, it has been associated with increased mortality, however, it has been used in late preterm infants successfully. Mild TH has been used in infants with necrotizing enterocolitis. For these infants TH was reported to be relatively safe with few major adverse effects observed. (22–24)

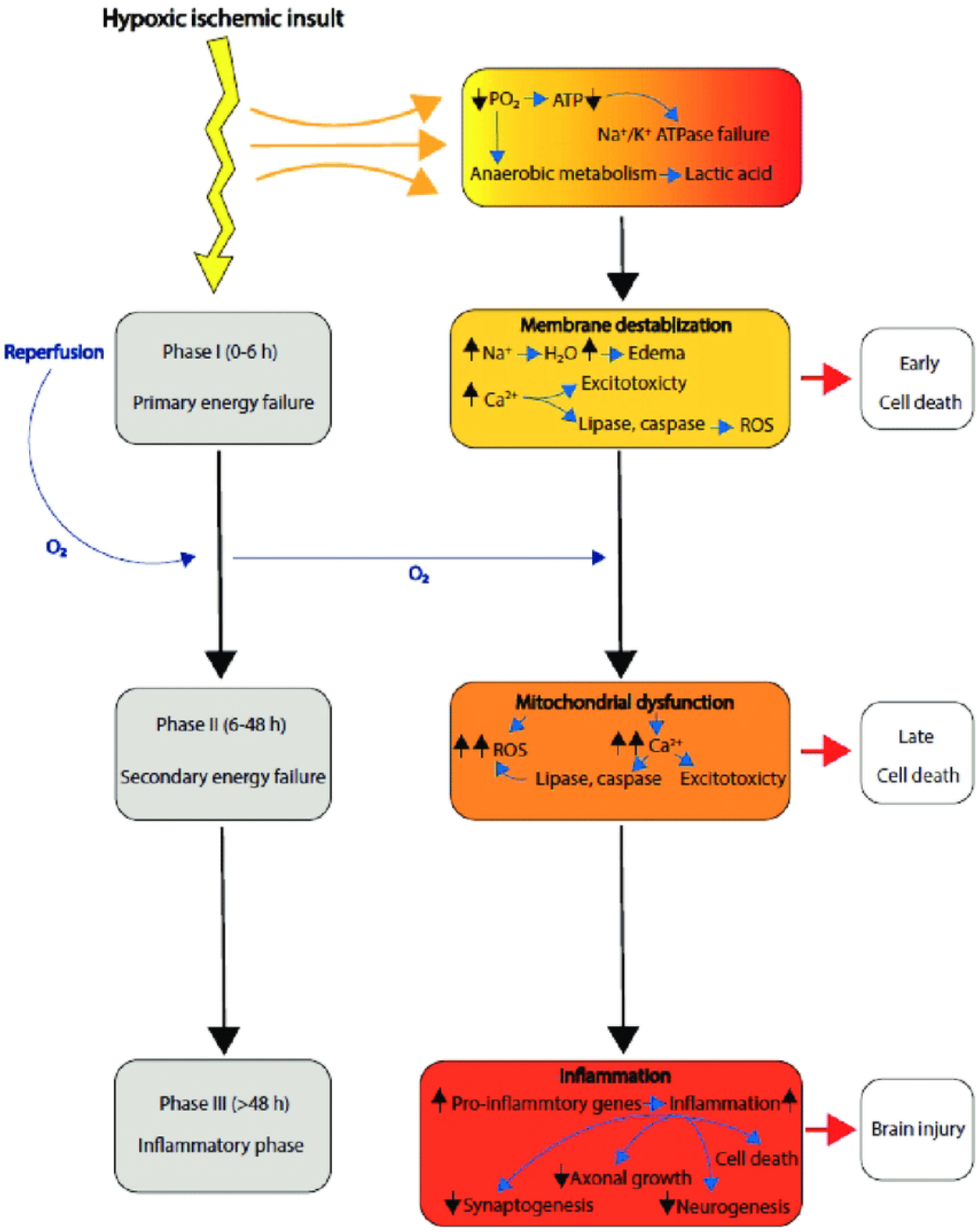

Figure 1: Pathophysiology of HIE

1.2 HIE and Electrolyte Derangements

Perinatal asphyxia is associated with several electrolyte derangements. Studies have shown that these derangements increase morbidity and mortality (25)

Newborns have hypernatremia due to several reasons. They have high insensible water losses through the skin, mucous membranes and respiratory tract and increased renal excretion of water. These lead to contraction of extracellular fluid. Neonates with HIE have hyponatremia due to increased secretion of anti-diuretic hormone (Syndrome of Inappropriate Anti-Diuretic Hormone Secretion). Hyponatremia (dilutional) occurs due to increased renal absorption of water. Hyponatremia in HIE also occurs due to the shift of sodium ions intracellularly.(26)

After birth, in the early newborn period, hyperkalemia is present due to movement of potassium from the intracellular space to the extracellular space. Potassium levels start to fall eventually due to excretion by the kidneys. Renal failure, which is a complication associated with perinatal asphyxia can result in hyperkalemia due to decreased potassium excretion. Metabolic acidosis is common finding in infants with perinatal asphyxia. To compensate, the surplus hydrogen ions are buffered in the cells via movement of potassium into the extracellular space which leads to relative hyperkalemia.(26)

At delivery, calcium transport across the placenta is terminated once the umbilical cord is cut. This causes plasma calcium levels to fall. Low calcium levels in blood stimulates production of parathyroid hormone (PTH) by the parathyroid glands and calcium is mobilized from bone leading to an increase in serum calcium. Newborns with HIE have a much slower response to the fall in calcium levels postnatally and do not secrete parathyroid hormone (PTH) as readily as the

newborns without HIE resulting in hypocalcemia. The intracellular shift of calcium ions also contributes to hypocalcemia (26)

In Nepal**,** a prospective study by Jitendra(26) on the prevalence of electrolyte disturbances on 88 asphyxiated infants found that infants with severe birth asphyxia had hyponatremia with mean serum sodium level of 127 meq/l, hyperkalemia, with mean serum potassium level of 6.7meq/L and hypocalcemia with mean serum calcium level of 0.9mmol/L. This study found a significant positive correlation between Apgar score at 5 minutes and serum sodium levels. Neonates with lower Apgar scores at 5 minutes had an increased incidence of hyponatremia and hyperkalemia.

A prospective cohort study in Estonia by Ilves(25) on 81 newborns assessed sodium, calcium and magnesium levels in infants with perinatal asphyxia and compared them with healthy term infants. It found that infants with severe HIE had hyponatremia, hypermagnesemia and hypocalcemia and that these electrolyte derangements were associated with poor outcomes in infants with perinatal asphyxia. The study recommended measurement and monitoring of serum electrolytes in infants with perinatal asphyxia routinely.

In India, a prospective study by Basu et al(12) assessed serum electrolytes in newborns with perinatal asphyxia and compared them with healthy term newborns. This study found that hyponatremia, hyperkalemia and hypocalcemia were more common in the asphyxiated newborns. The mean serum in the asphyxiated newborns was 122 mEq/L compared to 138 mEq/L in the control group. Mean serum potassium was 5.05 mEq/L in the asphyxiated newborns and 4.19 mEq/L in the control group. Mean serum calcium level was 6.85mg/dl in the asphyxiated newborns and 9.50 mg/dl in the control group. Newborns with lower Apgar scores at 5 minutes had higher incidences of hyponatremia, hypocalcemia and hyperkalemia. This is comparable to a study by Jitendra on prevalence of electrolyte disturbance in asphyxiated infants (15) which found that

neonates with lower Apgar scores at 5 minutes had an increased incidence of hyponatremia and hyperkalemia

1.3 Therapeutic Hypothermia and Electrolyte Derangements

Currently, Therapeutic Hypothermia (TH) is the only available treatment for neonates with moderate and severe HIE that has been shown to improve neurological outcomes. Therapeutic hypothermia is started within the first 6 hours of life. It is maintained for 72 hours at temperatures between 33℃ to 34°C with a target of 33.5℃ and started. It has three phases, induction, cooling and rewarming. Studies have shown that therapeutic hypothermia is neuroprotective and infants treated with TH have better neurodevelopmental outcomes at 24 months (6,27)

Hypothermia alters cellular functions. Some of these alterations, such as reduction in intracellular calcium, are neuroprotective. This alteration in cellular function while beneficial can result in several adverse effects. Studies have shown that these adverse effects start to occur when core body temperatures are less than 35°C.(28) There is paucity of data on the effect of therapeutic hypothermia on serum electrolytes.

1.3.1 Effect of Therapeutic Hypothermia on Serum Calcium

Hypocalcemia is common in infants with HIE. Therapeutic hypothermia (TH) decreases intracellular calcium influx. This prevents cellular apoptosis(which is caused by proteases and lipases released when calcium accumulates in the cells) and is neuroprotective (29).

In Canada, a historical, retrospective cohort analysis by Prempunpong et al (29) on serum calcium levels in newborns with moderate and severe HIE undergoing TH was conducted on 67 neonates. This study included a pre-Therapeutic Hypothermia group and a post-Therapeutic Hypothermia

group. During Therapeutic Hypothermia, a lower incidence of hypocalcemia was observed. The post-Therapeutic Hypothermia group needed lower calcium boluses to maintain normal calcium levels compared to the pre-Therapeutic Hypothermia group. The post-TH group had higher calcium levels on day 2 of life compared to the pre-TH group. This study concluded that TH resulted in higher serum calcium levels and exerted its neuroprotective effect by preventing intracellular accumulation of calcium thus increasing serum calcium levels in infants with HIE on TH

A retrospective cohort study in Calgary by Vayalthrikkovil(30) assessing the effect of TH on serum calcium was conducted on 113 newborns with moderate and severe HIE. 89 underwent TH, 24 did not undergo TH. TH was associated with an increase in serum calcium levels. The incidence of hypocalcemia was 12% in the TH group compared to 21% in the control group. Therapeutic Hypothermia was associated with hypercalcemia with 64% in the TH group compared to 33% in the control group.

1.3.2 Effect of Therapeutic Hypothermia on Serum Potassium

Hypothermia can result in variable electrolyte shifts. Some studies have shown instances of hypokalaemia in moderate hypothermia which is thought to be due to intracellular shift of potassium. Cellular loss of potassium due to severe hypothermia resulting in severe hypokalemia has been reported.(31) Severe hypokalemia poses the risk of development of arrhythmias.(32) As a result, there is need for monitoring during Therapeutic Hypothermia.

1.3.3 Effect of Therapeutic Hypothermia on Serum Sodium

Some studies have shown an association between therapeutic hypothermia and fluid retention resulting in dilutional hyponatremia(29) In 2019, a retrospective cohort study by Prempunpong(29) on the effect of therapeutic hypothermia on serum sodium levels, found that the incidence of hyponatremia increased from 48% before TH to 76% after TH. This study concluded that TH was followed by a higher incidence of hyponatremia and an increase in fluid retention.

Table 1: Studies on Serum Electrolytes in Therapeutic Hypothermia

Title /Author/Year	Setting	Type of study and Sample population	Findings
Serum calcium derangements and the impact of therapeutic hypothermia: Vayalthrikkovil et al 2018(30)	Level 3 NICU's in Calgary, Canada	A retrospective cohort study 113 neonates	TH was associated with higher serum calcium levels. In the TH group incidence of hypocalcemia was 12%. Incidence of hypocalcemia in the control group was 21%. Incidence of hypercalcemia was higher in the TH group,64%, compared to 33% in the control group
The effect of therapeutic hypothermia on fluid balance and incidence of hyponatremia Prempunpong et al 2015(29)	Montreal Children's Hospital Canada	Retrospective cohort study 67 neonates	TH was followed by a higher incidence of hyponatremia, 48% pre-TH to 76% post-TH. TH was associated with a higher incidence of fluid retention
Prevalence of electrolyte disturbances in perinatal asphyxia Jitendra et al 2018(26)	Bishweshwar Prasad Koirala Institute of Health Sciences Nepal	This prospective observational study 88 asphyxiated new-borns	Neonates with perinatal asphyxia had hyponatremia, hyperkalemia, and hypocalcemia. This increased morbidity and mortality.
Effect of Therapeutic Hypothermia on serum calcium concentration Prempunong et al 2015(29)	Montreal Children's Hospital Canada	Historical, retrospective cohort analysis. 67 neonates	Lower incidences of hypocalcemia were seen during TH. The post-TH group needed lower calcium boluses to maintain normal calcium levels compared to the pre-TH group. TH was associated with higher serum calcium levels
Clinico-Biochemical Correlation in Birth asphyxia and Its Effects and Outcomes Basu et al(12)	Odisha State, India 2014-2016	Prospective cohort study 150 babies	Neonates with perinatal asphyxia had hyponatremia, hypocalcemia and hyperkalemia.
Serum magnesium and calcium concentrations in asphyxiated term newborn infants with HIE Ilves et al 1997(25)	University of Tartu Estonia	Prospective cohort study 81 infants	Infants with severe HIE had hyponatremia, hypermagnesemia and hypocalcemia. These derangements were associated with poor outcome. The study recommended routine determination electrolytes in asphyxiated infants.

1.4 Study Justification and Utility

Therapeutic Hypothermia is now the standard treatment of moderate and severe hypoxic ischaemic encephalopathy (HIE).(6) This form of treatment has been given in KNH NBU since 2018. This study aims to establish the serum sodium, calcium and potassium levels in babies with moderate and severe HIE and to compare these electrolyte levels with babies with moderate and severe HIE not undergoing TH at KNH. Therapeutic hypothermia has been associated with adverse derangements in electrolytes in some studies. The results will inform better monitoring and care of these babies. There is paucity of literature on electrolyte disturbances associated with Therapeutic Hypothermia and findings from this study will add to this information.

2. STUDY OBJECTIVES

2.1 Research Question

Does Therapeutic Hypothermia have significant impact on serum electrolytes in neonates with moderate and severe HIE in KNH NBU?

2.2 Primary Objective

To determine the effect of Therapeutic Hypothermia on sodium, calcium and potassium levels in neonates with moderate and severe HIE in Kenyatta National Hospital

2.3 Secondary Objective

To compare sodium, calcium and potassium levels in neonates with moderate and severe HIE undergoing Therapeutic Hypothermia to those with moderate and severe HIE not undergoing Therapeutic Hypothermia

3. Methodology

3.1 Study design

This was a hospital based prospective cohort study.

3.2 Study Site

This study was conducted at the NBU Kenyatta National hospital. This is one of the referral hospitals in Kenya. It is situated in Nairobi County and receives patients from across the country. All sick newborns born at KNH are admitted to this unit. Referrals from other facilities are also admitted. The unit is staffed by 5 neonatologists, 7 Neonatology fellows, pediatric residents and nurses

The Machine used for cooling is the MiraCradle Neonate Cooler and the cooling procedure is whole body cooling. Currently there are only two machines available for cooling at this facility

Selection Criteria for Therapeutic Hypothermia at KNH NBU

i. Gestation 36 weeks
ii. Age less than 6 hours from birth
iii. Apgar score of less than 5 at 10 minutes
iv. Moderate or severe HIE based on the Sarnat and Sarnat Score
v. Neurological signs- Seizures, hypotonia, hypertonia, weak/absent reflexes

3.3 Study Population

The study included neonates with moderate and severe HIE admitted to the KNH Newborn unit (NBU)

3.4 Sample Size

Sample size was calculated using Fleiss sample size calculation for proportions. The proportions used were determined using a similar study by Vayalthrikkovil(30) on Serum calcium derangements in neonates with moderate to severe hypoxic ischemic encephalopathy and the impact of therapeutic hypothermia

$$N_1 = \left\{ z_{1-\alpha/2} * \sqrt{\bar{p} * \bar{q} * (1 + \frac{1}{k})} + z_{1-\beta} * \sqrt{p_1 * q_1 + (\frac{p_2 * q_2}{k})} \right\}^2 / \Delta^2$$

$$q_1 = 1 - p_1$$

$$q_2 = 1 - p_2$$

$$\bar{p} = \frac{p_1 + kp_2}{1 + K}$$

$$\bar{q} = 1 - \bar{p}$$

$$N_1 = \left\{ 1.96 * \sqrt{0.485 * 0.515 * (1 + \frac{1}{1})} + 0.84 * \sqrt{0.64 * 0.36 + (\frac{0.33 * 0.67}{1})} \right\}^2 / 0.31^2$$

$$N_1 = 40$$

$$N_2 = K * N_1 = 40$$

p_1, p_2 = proportion (incidence) of groups #1 and #2
$\Delta = |p_2 - p_1|$ = absolute difference between two proportions
n_1 = sample size for group #1
n_2 = sample size for group #2
α = probability of type I error (usually 0.05)
β = probability of type II error (usually 0.2)
z = critical Z value for a given α or β
K = ratio of sample size for group #2 to group #1

With a finite population correction factor of 0.83 and an attrition correction factor of 1.1 giving a final sample size of **37** in each group.

3.5 Study Period

The study was carried out over a period of 5 months between 1st September 2022 and 28th January 2023

3.6 Recruitment of Study Participants

Infants with moderate and severe HIE based on the Sarnat and Sarnat score were recruited into the study. The Sarnat and Sarnat score was done by the NBU admitting doctor on all neonates with perinatal asphyxia at the KNH NBU. Those with moderate and severe HIE who met the criteria for Therapeutic Hypothermia were started on Therapeutic Hypothermia subject to availability of the MiraCradle cooling devices. Gestational age assessment was done by the principal investigator on all infants using the New Ballard Score for Gestational Age Assessment. Infants with gestational age of 36 weeks and above included in the study.

3.6.1 Cohort on Therapeutic Hypothermia

Inclusion criteria

- Newborn infants born at 36 weeks or more gestation
- Neonates with Moderate or Severe HIE according to the Sarnat and Sarnat Criteria (appendix 1)
- Consent obtained from the guardian

Exclusion criteria

- Severe chromosomal or congenital anomalies.
- Preterm neonates less than 36 weeks gestational age

3.6.2 Cohort not on Therapeutic Hypothermia

Inclusion criteria

- Newborn infants born at 36 weeks or more gestation
- Neonates with Moderate or Severe HIE according to the Sarnat and Sarnat Criteria (appendix 1)
- Infant meets the selection criteria for Therapeutic Hypothermia but not on therapy due to unavailability of cooling devices. (KNH NBU currently only has 2 cooling devices available)
- Consent obtained from the guardian

Exclusion criteria

- Severe chromosomal or congenital anomalies.
- Preterm neonates less than 36 weeks gestational age

3.7 Study Procedures

3.7.1 Sampling Techniques

Newborns that satisfied the inclusion criteria were enrolled into the study until the sample size was achieved. Written informed consent was obtained from parents/guardians.

For the therapeutic hypothermia group, samples for serum calcium, sodium and potassium were collected on day 1, day 2 (maintenance phase) and day 4 (rewarming phase) of life.

For the non-therapeutic hypothermia group samples were collected on day 1, day 2 and day 4 of life. 1ml of blood was collected into a vacutainer via venipuncture of the cubital vein. Results were recorded in a questionnaire.

3.7.2 Blood Sample Collection Procedure

Infection prevention measures were instituted including those of COVID 19. All the samples were collected by the principal investigator and a qualified research assistant trained by the principal investigator. Samples were collected as 1mls in a Red-top tube. The sample and request forms were filled using double identifiers, date and time of collection. The samples were delivered to the Biochemistry laboratory within 30 minutes of extraction.

3.7.3 Specimen Handling and Analysis

The sample was processed and analysed using the HUMASTAR 600 machine. Specimen was received in the lab by a health records officer and assigned a lab number. The specimen was centrifuged and serum obtained. Serum was analysed in the HUMASTAR 600 machine. Results were recorded and dispatched to the ward.

3.7.4 Quality Control

The machine has internal quality control checks done daily by laboratory personnel. External quality control is done every 2 months by the Human Quality Assessment Services.

3.7.5 Laboratory Results handling

The test results were picked from the laboratory, the information counterchecked with the subject data before being entered into the spreadsheet. In the case of any abnormal values, the researcher or her assistant immediately informed the clinical team for review and timely intervention.

Rejected samples were noted and recollected within in the stipulated time period.

3.7.6 Study Flow Diagram

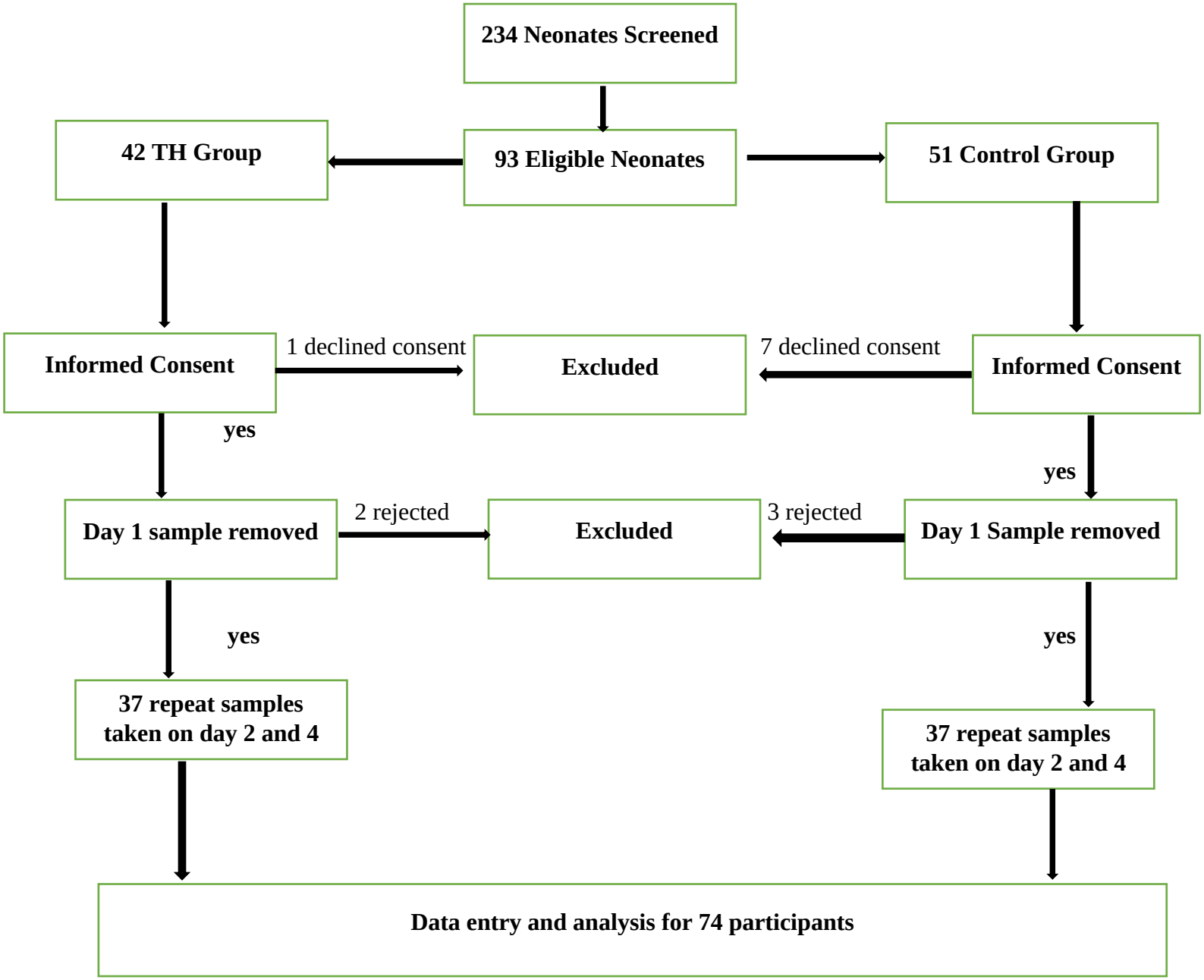

Figure 2: Study Flow Diagram

3.7.7. Data Collection

All term neonates admitted at KNH NBU for moderate to severe HIE were assessed by the principal investigator or research assistant. The findings were recorded in a data collection tool. Gestational age, sex, birth weight, mode of delivery, respiratory rate, heart rate, APGAR score at 1 and 5 minutes was recorded. Fluid intake and urine output was be recorded daily. Calcium, sodium and potassium levels were documented on day 1, day 2 and day 4 of life for both the Therapeutic Hypothermia group and the no Therapeutic Hypothermia group. Maternal biodata including age, parity, marital status, duration of labour and history of hypertension/endocrine disorders was recorded.

4. DATA MANAGEMENT, RESULTS AND ANALYSIS

4.1 DATA MANAGEMENT

Data recorded in questionnaires was collated into a cloud-based spreadsheet form. Data quality was done using scripts looking for inappropriate duplicates, outliers and missing values. Data analysis was then done using R Software version 4.2.2.

Categorical variables were analysed using proportions and presented in tables and charts where appropriate. Continuous variables were tested for normality using the Shapiro Wilk test and visually using the QQ plot. Normally distributed data was measured for centrality and dispersion using mean and standard deviation respectively while non normal data used median and Inter Quartile Range respectively.

Inferential analysis was done on the trend of the electrolytes across the cooling and rewarming phase using paired T test. Further analysis was done where day 1 ,2 and 4 Calcium, Potassium and Sodium values for both groups were analysed using the 2 sample T test for between group differences.

Predictors of the changes in electrolytes was done using Pearson's correlation and iterations of simple and multiple linear or logistic regression as appropriate. The dependent variable was each electrolyte with the independent variables being derived from the biodata, vitals, fluid intake and management. Moderator analysis was done for possible confounders to the primary outcome variables.

The results were presented as summary statistics, tables and graphs.

4.2 RESULTS

During the study a total of 234 neonates were screened for eligibility over a duration of 5 months. 156 were excluded for not meeting the inclusion criteria. 5 samples were rejected and 6 deaths were recorded during the study period. Neonates who had received electrolyte supplementation before day 1 of life (baseline) blood samples could be drawn were excluded from this study. A total of 74 subjects were enrolled, 37 who had therapeutic hypothermia and 37 without therapeutic hypothermia

4.1 Neonatal and Maternal Demographic Characteristics

The descriptive analysis of the TH and No TH group revealed similar biodata profiles with statistically non-significant differences in sex, mode of delivery, Sarnat staging, maternal status, maternal hypertension and maternal endocrine disease. Place of delivery had a statistically significant difference between the two groups.

The mean birth weight in the TH group was 3140 gms while the control group was 3222 gms ($t(72) = 0.85, p = .395$). Both groups were predominantly male at 62% in the TH group and 68% in the no TH group ($X^2 = 0.42, p = .5134$).

The Sarnat stage 2 and 3 for the groups was 81% and 19% for the TH group and 92% and 8% for the no TH group respectively ($X^2 = 1.04, p = .3077$). The place of delivery in the TH group was 92% at Kenyatta hospital and 8% at other facilities while in the no TH group 14% were from Kenyatta National Hospital while 86% were from other facilities ($X^2 = 42.5, p = .0001$).

In terms of the maternal status at enrollment, 92% of the TH group were enrolled in a stable state while 100% of the no TH group were stable ($X^2 = 1.38, p = .2385$).

Both groups had similar profiles of maternal endocrine disorder at 3% ($X^2 = 0.2$, $p = .9089$). 11% of mothers in the TH group had a history of hypertension in the TH group while the no TH group had 5% ($X^2 = 0.18$, $p = .6702$).

Table 2: Biodata of neonates with moderate and severe HIE at KNH

		Therapeutic hypothermia group	Control group	P value
Birth weight (mean in gms)		3140(398.3)	3222(417.5)	0.3950[a]
Sex	Male	23(62%)	25(68%)	0.8076[b]
	Female	14(38%)	12(32%)	
Mode of Delivery	SVD	30(81%)	33(89%)	0.5134[b]
	CS	7(19%)	4(11%)	
Place of Delivery	KNH	34(92%)	5(14%)	0.0001[b]
	Referral	3(8%)	32(86%)	
Maternal status at enrollment	Stable	34(92%)	37(100%)	0.2385 [b]
	Critical	3(8%)	0(0%)	
History of endocrine disease	No	36(97%)	36(97%)	0.6702 [b]
	Yes	1(3%)	1(3%)	
History of hypertension	No	33(89%)	35(95%)	0.9089 [b]
	Yes	4(11%)	2(5%)	
Sarnat Stage	Stage 2	30(81%)	34(92%)	0.3077 [b]
	Stage 3	7(19%)	3(8%)	

[a] Unpaired T Test, [b] Pearson's Chi-squared test with Yates' continuity correction,

4.2 Clinical Characteristics

The heart rate was taken at day 1, 2 and 4. The mean day 1 heart rate was statistically different between the two groups with the TH group having 128 bpm and the no TH group having 139 bpm (*t (70.4) = 2.68, p = .0090*). Similarly, the mean day 2 heart rate was statistically different between the two groups with the TH group having 90 bpm and the no TH group having 137 bpm

(*t (70.7) = 30.4, p = .0001*). The mean day 4 heart rate was statistically similar for the two groups at 133 bpm and 136 bpm for TH and no TH groups respectively (*t (67.3) = 1.32, p = .1903*).

The respiratory rate was taken at day 1, 2 and 4. The mean day 1 respiratory rate was statistically different between the two groups with the TH group having 43 brpm and the no TH group having 50 brpm (*t (70.5) = 2.27, p = .0259*). The mean day 2 respiratory rate was not statistically different between the two groups with the TH group having 40 brpm and the no TH group having 45 brpm (*t (67.6) = 1.89, p = .0633*). The mean day 4 respiratory rate was statistically similar for the two groups at 133 bpm and 136 bpm for TH and no TH groups respectively (*t (68.1) = 1.33, p = .1853*).

Table 3: Heart rate of neonates with moderate and severe HIE at KNH

Mean (SD)	Therapeutic hypothermia group	Control group	P value
Heart rate Day 1	128.4(18.6)	139.2(16.0)	0.0090
Heart rate Day 2	90.2(6.2)	136.9(7.0)	0.0001
Heart rate Day 4	133.2(10.6)	136.1(8.1)	0.1903

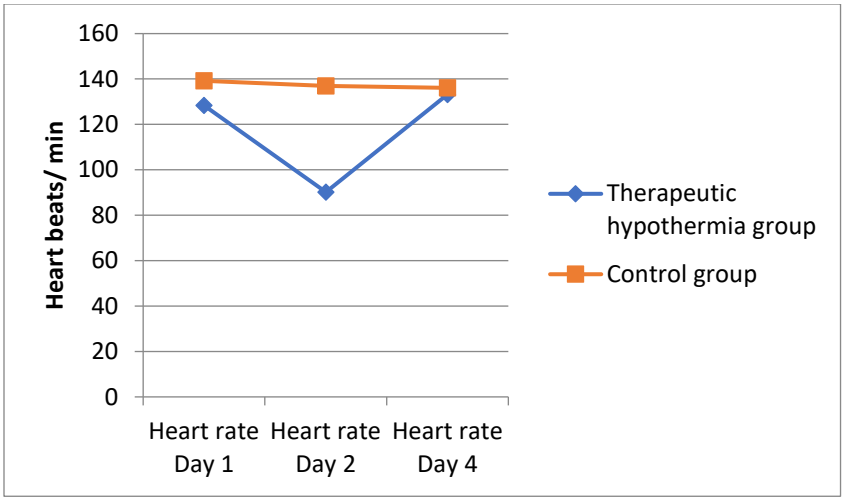

Figure 3: Heart rate of neonates with severe HIE at KNH

4.1.1 Fluid Intake

The median day 1 fluid intake was 126 mls for the TH group 127 mls for the no TH group (*mann-u = 726.5, p = .6533*). The median day 2 fluid intake was 183 mls for the Th group and 190 mls for the no TH group (*mann-u = 852.5, p = .0700*). The median day 3 fluid intake was 244 mls for the Th group and 254 mls for the no TH group (*mann-u = 855, p = .0659*). The median day 4 fluid intake was 305 mls for the Th group and 317 mls for the no TH group (*mann-u = 851.5, p = .0717*).

Table 4: Total Daily Fluid Intake of neonates with moderate and severe HIE at KNH

Median (IQR)	Therapeutic hypothermia group	Control group	P value
Fluid Day 1	126ml (13)	127ml (16)	0.6533
Fluid Day 2	183ml (29)	190ml (24)	0.0700
Fluid Day 3	244ml (40)	254ml (40)	0.0659
Fluid Day 4	305ml (47)	317ml (50)	0.0717

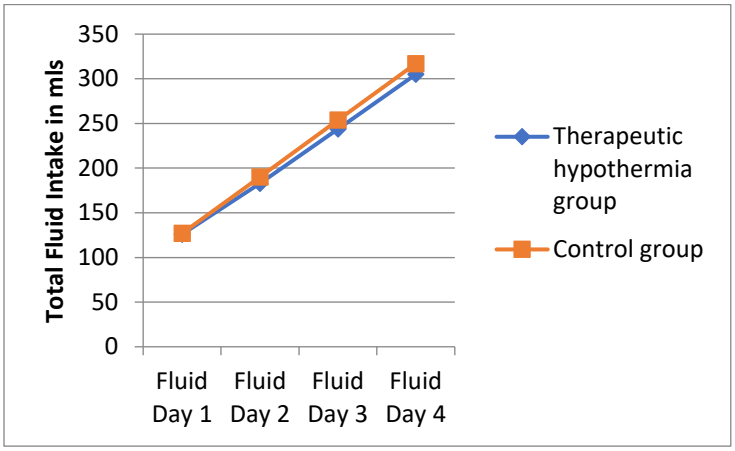

Figure 4: Chart Total Daily Fluid intake of neonates with moderate and severe HIE at KNH

4.1.2 Urine output

Table 5: Urine output of neonates with moderate and severe HIE at KNH

Median (IQR)	Therapeutic hypothermia group	Control group
Urine Output Day 1	11ml (10)	23ml (19)
Urine Output Day 2	44ml (23)	37ml (14)
Urine Output Day 3	67ml (21)	63ml (22)
Urine Output Day 4	69ml (15)	78ml (19)

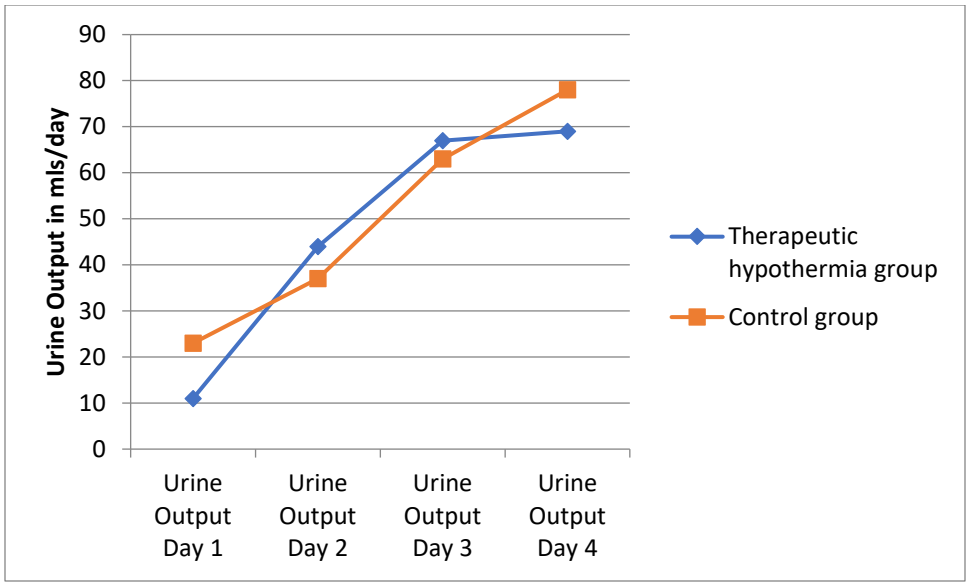

Figure 5: Urine output of neonates with moderate and severe HIE at KNH

4.2 Electrolyte trend in neonates undergoing Therapeutic Hypothermia

4.2.1 Calcium

On day 1, which was the baseline phase, the mean calcium level was 1.99 ± 0.19 mmol/L. There was no mean difference or p value available for this phase as it served as the reference point.

During the cooling phase on day 2, the mean calcium level increased to 2.15 ± 0.22 mmol/L. The mean difference between the baseline and the cooling phase was 0.16 mmol/L, and this difference was statistically significant ($p < 0.0001$).

On day 4, during the rewarming phase, the mean calcium level further increased to 2.35 ± 0.23 mmol/L. The mean difference between the rewarming and the cooling phase was 0.2 mmol/L, and this difference was also statistically significant ($p < 0.0001$).

The study observed significant changes in calcium levels in neonates undergoing therapeutic hypothermia, with increases in calcium levels during both the cooling and rewarming phases compared to the baseline.

Table 6: Trend of mean calcium in neonates undergoing Therapeutic Hypothermia

Sampling date	Phase	Calcium(mean/SD)	Mean Difference	P value
Day 1	Baseline	1.99mmol/L (0.19)	-	-
Day 2	Cooling	2.15mmol/L (0.22)	0.16	<0.0001
Day 4	Rewarming	2.35mmol/L (0.23)	0.2	<0.0001

4.2.2 Sodium

On day 1, which was the baseline phase, the mean sodium level was 131.62 ± 6.59 mmol/L. There was no mean difference available for this phase as it served as the reference point.

During the cooling phase on day 2, the mean sodium level slightly increased to 132.51 ± 5.10 mmol/L. The mean difference between the baseline and the cooling phase was 0.89 mmol/L, but this difference was not statistically significant (p = 0.5).

On day 4, during the rewarming phase, the mean sodium level increased further to 135.65 ± 4.72 mmol/L. The mean difference between the rewarming and the cooling phase was 3.1 mmol/L, and this difference was statistically significant (p = 0.0008).

While there was a slight increase in sodium levels during the cooling phase compared to the baseline, this difference was not statistically significant. However, a significant increase in sodium levels was observed during the rewarming phase compared to the baseline.

Table 7: Trend of mean sodium in neonates undergoing Therapeutic Hypothermia

Sampling date	Phase	Sodium(mean/SD)	Mean Difference	P value
Day 1	Baseline	131.62mmol/L (6.59)	-	-
Day 2	Cooling	132.51mmol/L (5.10)	0.89	0.5
Day 4	Rewarming	135.65mmol/L (4.72)	3.1	0.0008

4.2.3 Potassium

On day 1, which was the baseline phase, the mean potassium level was 5.72 ± 1.11 mmol/L. There was no mean difference available for this phase as it served as the reference point.

During the cooling phase on day 2, the mean potassium level decreased to 4.63 ± 0.68 mmol/L. The mean difference between the baseline and the cooling phase was -1.09 mmol/L, and this difference was statistically significant ($p < 0.0001$).

On day 4, during the rewarming phase, the mean potassium level further decreased to 4.27 ± 0.78 mmol/L. The mean difference between the rewarming and the cooling phase was -0.36 mmol/L, and this difference was statistically significant ($p = 0.0113$).

In summary, the study observed significant changes in potassium levels in neonates undergoing therapeutic hypothermia, with decreases in potassium levels during both the cooling and rewarming phases compared to the baseline.

Table 8: Trend of mean potassium in neonates undergoing Therapeutic Hypothermia

Sampling date	Phase	Potassium(mean/SD)	Mean Difference	P value
Day 1	Baseline	5.72mmol/L (1.11)	-	-
Day 2	Cooling	4.63mmol/L (0.68)	-1.09	<0.0001
Day 4	Rewarming	4.27mmol/L (0.78)	-0.36	0.0113

4.3 Analysis of electrolytes between the Therapeutic Hypothermia group and no therapeutic hypothermia group

4.3.1 Serum Calcium

The mean day 1 calcium level was not statistically significant at 1.99mmol/L (SD - 0.19) and 1.95 mmol/L (SD - 0.29) for TH and no TH respectively (*t (62.1) = -0.76, p = .4473*). The mean day 2 calcium levels for TH was 2.15 mmol/L (SD - 0.22) and for no TH 2.09 mmol/L (SD - 0.23) and similarly was not statistically significant (*t (71.9) = -1.1, p = .2640*). The mean day 4 calcium level was statistically different between the two groups at 2.35mmol/L (SD - 0.23) and 2.19 mmol/L (SD - 0.23) for TH and no TH respectively (*t (71.9) = -2.94, p = .0043*).

Table 9: Serum Calcium in neonates with moderate and severe HIE at KNH

Mean (SD)	Therapeutic hypothermia group	Control group	P value
Calcium Day 1(mean/SD)	1.99mmol/L (0.19)	1.95mmol/L (0.29)	0.4473
Calcium Day 2(mean/SD)	2.15mmol/L (0.22)	2.09mmol/L (0.23)	0.2640
Calcium Day 4(mean/SD)	2.35mmol/L (0.23)	2.19mmol/L (0.23)	0.0043

*Two sample T Test

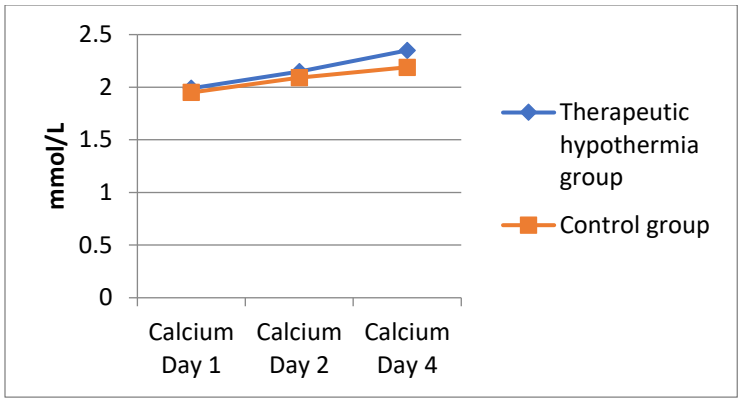

Figure 6: Serum Calcium in neonates with moderate and severe HIE at KNH

Hypocalcaemia as defined by serum calcium levels of less than 2 mmol/L was analysed using percentages and odds ratios. Hypocalcaemia in Day 1was seen in 72.9% of the TH group subjects and 70.3% of the no TH group subjects but was not statistically different between the groups (*OR 0.98, CI 95%, 0.55-1.41*). Day 2 hypocalcaemia reduced in both groups to 40.5% in TH and 45.9% in the no TH group but the odds of hypocalcaemia remained statistically the similar in both groups (*OR 0.63, CI 95%, 0.195-1.07*). Day 4 hypocalcaemia reduced further in both groups to 5.4% in the TH group and 29.7% in the no Th group. Here the difference between the two groups was statistically significant with an odds ratio of 0.15 (95% Confidence Interval 0.01 – 0.94).

No subject had hypercalcaemia defined as a serum calcium of >3 mmols in both groups at day 1, 2 and 4.

Table 10: Odds ratio of hypocalcemia

Hypocalcaemia <2	Therapeutic hypothermia group (Percentage)	No TH group	Odds ratio	95% Confidence interval
Calcium Day 1	27(72.9%)	26(70.3%)	0.98	0.55-1.41
Calcium Day 2	15(40.5%)	17(45.9%)	0.63	0.19-1.07
Calcium Day 4	2(5.4%)	11(29.7%)	0.15	0.01-0.94

4.3.2 Sodium

The mean day 1 sodium level was not statistically significant at 131.6 mmol/L (SD 6.59) and 130.6 mmol/L (SD 5.66) for TH and no TH respectively (*t (70.4) = -0.71, p = .4743*). The mean day 2 sodium levels for TH was 132.5 mmol/L (SD 5.10) and for no TH 131.7 mmol/L (SD 5.54) and similarly was not statistically significant (*t (71.4) = -0.6, p = .4871*). The mean day 4 sodium level was not statistically different between the two groups at 135.7 mmol/L (SD 4.72) and 136.0 mmol/L (SD 5.58) for TH and no TH respectively (*t (70.5) = 0.27, p = .7879*).

Table 11: serum Sodium in neonates with moderate and severe HIE at KNH

Mean (SD)	Therapeutic hypothermia group	Control group	P value
Sodium Day 1	131.62mmol/L (6.59)	130.59mmol/L (5.66)	0.4743
Sodium Day 2	132.51mmol/L (5.10)	131.65mmol/L (5.54)	0.4871
Sodium Day 4	135.65mmol/L (4.72)	135.97mmol/L (5.58)	0.7879

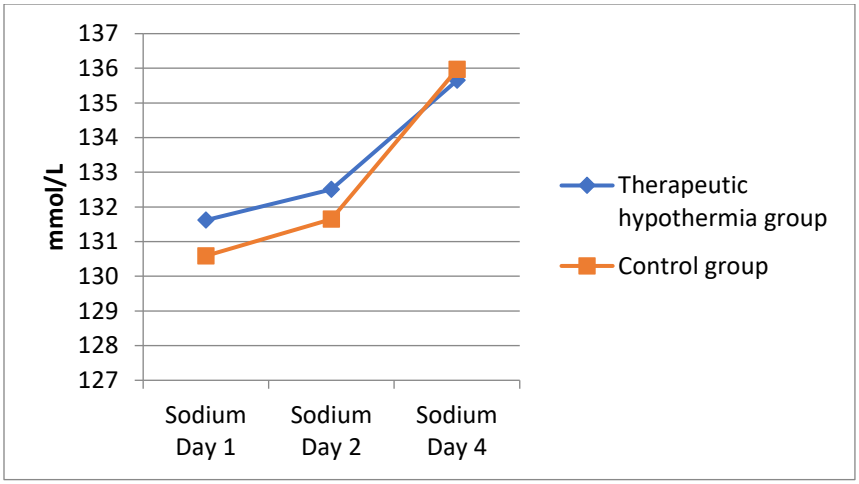

Figure 7: Serum Sodium in neonates with moderate and severe HIE at KNH

Hyponatraemia as defined by serum calcium levels of less than 128 mmol/L was analysed using percentages and odds ratios. Hyponatraemia in Day1 was equal for the TH and no TH groups at 35.1% (*OR 1, CI 95%, 0.39-2.59*). Day 2 hyponatraemia reduced in both groups to 10.8% in TH and 24.3% in the no TH group but the odds of hyponatraemia remained statistically non-significant in both groups (*OR 0.38, CI 95%, 0.11-1.36*). Day 4 hyponatraemia reduced further in both groups to 0% in the TH group and 8.1% in the no TH group.

Hypernatraemia was seen in only one subject in the TH group on Day 1 and Day 4. No subject had hypernatraemia in either group on Day 2.

Table 12: odds ratio of hyponatraemia

Hyponatraemia <128	Therapeutic hypothermia group	Control group	Odds ratio	95% Confidence Interval
Sodium Day 1	13 (35.1%)	13 (35.1%)	1	0.39-2.59
Sodium Day 2	4 (10.8%)	9 (24.3%)	0.38	0.11 – 1.36
Sodium Day 4	0 (0%)	3 (8.1%)	NA	NA

4.3.3 Potassium

The mean day 1 potassium level was not statistically significant at 5.72mmol/L (SD 1.11) and 5.65 mmol/L (SD 1.14) for TH and no TH respectively (*t (71.9) = -0.26, p = .7927*). The mean day 2 potassium levels for TH was 4.63 mmol/L (SD 0.68) and for no TH 4.62 mmol/L (SD 0.68) and similarly was not statistically significant (*t (71.9) = -0.1, p = .9318*). The mean day 4 potassium level was not statistically different between the two groups at 4.27mmol/L (SD 0.78) and 4.08 mmol/L (SD 0.6) for TH and no TH respectively (*t (67.5) = -1.2, p = .2419*).

Table 13: Mean Serum Potassium in neonates with moderate and severe HIE at KNH

Mean (SD)	Therapeutic hypothermia group	Control group	P value
Potassium Day 1	5.72mmol/L (1.11)	5.65mmol/L (1.14)	0.7927
Potassium Day 2	4.63mmol/L (0.68)	4.62mmol/L (0.68)	0.9318
Potassium Day 4	4.27mmol/L (0.78)	4.08mmol/L (0.6)	0.2419

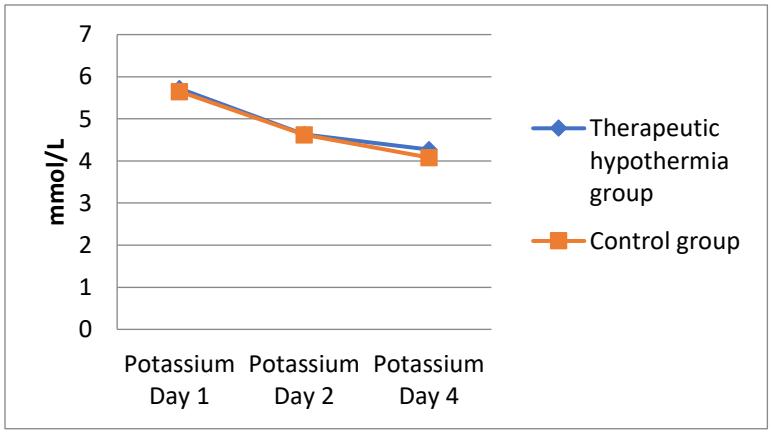

Figure 8: Mean Serum Potassium in neonates with moderate and severe HIE at KNH

Hypokalemia was seen on one TH subject in Day 1 and one no TH subject on Day 4. There was no patient with hypokalemia on Day 2.

Hyperkalemia as defined by serum calcium levels of more than 6 mmol/L was analysed using percentages and odds ratios. Hyperkalemia in Day1 was 48.6% in the TH group and 35.1% in the no Th group. The odds ratio of hyperkalemia on Day 1 was statistically significant with a 78% increased likelihood in the TH (*OR 1.78, CI 95%, 1.32 -2.24*). Day 2 hyperkalemia reduced in both groups to 2.7% in TH and 8.1% in the no TH group but the odds of hyperkalemia remained statistically non-significant in both groups (*OR 0.33, CI 95%, 0.01-1.49*). Day 4 hyperkalemia reduced further in both groups to 2.7% in the TH group and 0% in the no TH group.

Table 14: Odds ratio of hyperkalemia

Hyperkalemia >6	Therapeutic hypothermia group (percentage)	Control group (percentage)	Odds ratio	95% Confidence Interval
Potassium Day 1	18(48.6%)	13(35.1%)	1.78	1.32-2.24
Potassium Day 2	1(2.7%)	3(8.1%)	0.33	0.01-1.49
Potassium Day 4	1(2.7%)	0(0%)	NA	NA

4.4 Correlation analysis

Correlation between the continuous variables was done iteratively. The dependent/outcome variables tested were potassium, calcium and sodium levels for Day 1, 2 and 4. The independent or predictor variables used were day 1, 2 3 and 4 values for weight, total fluid intake, normal saline intake, potassium intake, expressed breastmilk intake and urine output.

Where the data was normally distributed, Pearson's correlation was used while where it was non normal Spearman correlation was used. No iteration with the outcome variables had a moderate or strong correlation with the electrolytes where all correlation coefficients being less than 0.5.

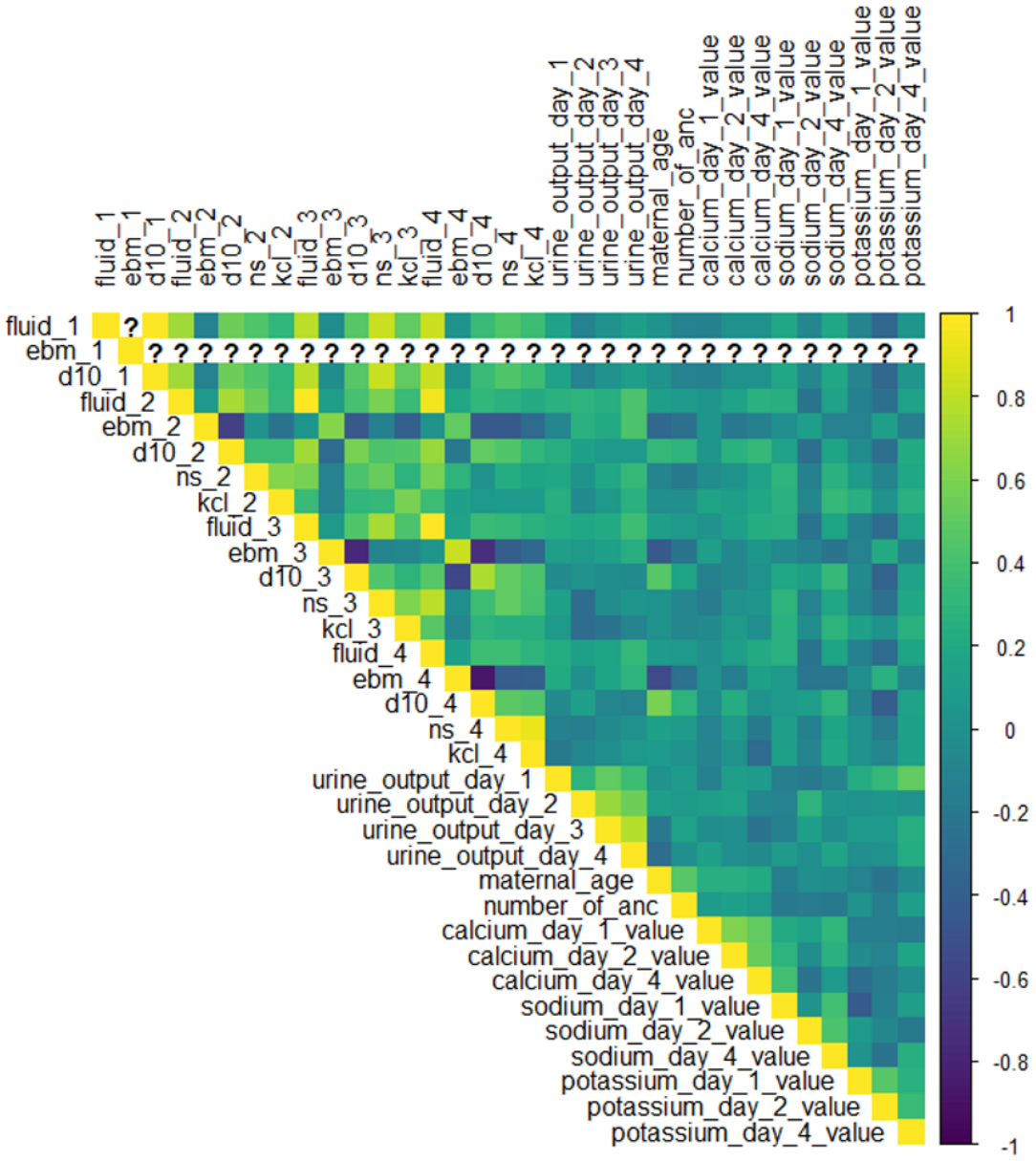

Figure 9: Correlation plot of continuous variables

Simple linear regression was done iteratively with each serum electrolyte (Sodium, Potassium, Calcium) as the dependent or outcome variable and the intervention (Therapeutic hypothermia, no Therapeutic hypothermia) as the independent or predictor variable. Demographic characteristics, clinical features and fluid intake were used as moderating factors. No regression iteration model had an adjusted R squared of more than 0.3 or acceptable residual standard errors showing a poor fit. Since the indicators showed a poor fit of the regression model, no interpretation of the model values was done.

5. DISCUSSION

In this study we explored the effect of Therapeutic Hypothermia on serum electrolytes (calcium, sodium and potassium) in infants with moderate and severe HIE. Therapeutic hypothermia did not result in further derangements of sodium, potassium and calcium levels from baseline. It was associated with lower incidence of hyperkalemia, hyponatremia and hypocalcemia.

The descriptive analysis of the TH and No TH group revealed similar biodata profiles with statistically non-significant differences in sex, mode of delivery, Sarnat staging, maternal status, maternal hypertension and maternal endocrine disease. This was important to avoid selection bias at enrolment.

Place of delivery had a statistically significant difference between the two groups with 92% of those who received TH being delivered in KNH and 8% being referred. In the no TH group 18% were delivered in KNH and 86% were referrals. This can be explained by the fact that infants with HIE who were delivered in KNH were more likely to receive TH compared to referrals due to the limited number of cooling devices (2) available at the KNH NBU.

Fluid and electrolyte supplementation may affect the electrolyte values therefore daily fluid and electrolyte intake was recorded for all participants and compared with the electrolyte values. There was no significant difference in the fluid and electrolyte intake in the TH and no TH group. Subjects who had prior documented electrolyte supplementation before day 1 of life (baseline) blood samples could be drawn were not included in this study.

The heart rate was taken at day 1, 2 and 4. The mean day 1 heart rate was statistically different between the two groups with the TH group having 128 bpm and the no TH group having 139 bpm. Similarly, the mean day 2 heart rate was statistically different between the two groups with the TH group having 90 bpm and the no TH group having 137 bpm. The mean day 4 heart rate was statistically similar for the two groups at 133 bpm and 136 bpm for TH and no TH groups respectively.

The lower heart rate in the TH group on day 2 (cooling phase) is an expected side effect during TH. Studies have shown increased incidence of bradycardia during TH. This reduces during the rewarming phase (16)

The primary objective was to determine the effect of Therapeutic hypothermia on serum sodium, calcium and potassium. At baseline, the mean calcium level was 1.99 ± 0.19 mmol/L. This increased to 2.15 ± 0.22 mmol/L on day 2 during the cooling phase. The mean difference between the baseline and the cooling phase was 0.16 mmol/L, and this difference was statistically significant ($p < 0.0001$).

On day 4, during the rewarming phase, the mean calcium level further increased to 2.35 ± 0.23 mmol/L with a mean difference of 0.2 mmol/L, which was statistically significant ($p < 0.0001$).

The study observed significant changes in calcium levels in neonates undergoing therapeutic hypothermia, with increases in calcium levels during both the cooling and rewarming phases compared to the baseline. Similar trends have been observed in other studies(29,30)

On day 1, the mean sodium level was 131.62 ± 6.59 mmol/L. This increased to 132.51 ± 5.10 mmol/L during the cooling phase on day 2. The mean difference between the baseline and the cooling phase was 0.89 mmol/L, but this difference was not statistically significant ($p = 0.5$). On day 4, during the rewarming phase, the mean sodium level increased further to 135.65 ± 4.72 mmol/L. The mean difference between the rewarming and the cooling phase was 3.1 mmol/L, and this difference was statistically significant ($p = 0.0008$).

On day 1, which was the baseline, the mean potassium level was 5.72 ± 1.11 mmol/L. This decreased to 4.63 ± 0.68 mmol/L during the cooling phase on day 2. The mean difference between the baseline and the cooling phase was -1.09 mmol/L, and this difference was statistically significant ($p < 0.0001$). On day 4, during the rewarming phase, the mean potassium level further decreased to 4.27 ± 0.78 mmol/L. The mean difference between the rewarming and the cooling phase was -0.36 mmol/L, and this difference was statistically significant ($p = 0.0113$).

Overall, compared to baseline levels at day 1, neonates undergoing therapeutic hypothermia had higher mean calcium, higher mean sodium levels and lower mean potassium levels during both cooling and rewarming phases, with more significant changes in the rewarming phase. None of

the five major RCTs on TH, namely Cool cap, NICHD, neo.EURO.network, ICE, and TOBY trials reported significant changes in serum calcium, sodium and potassium levels during cooling (33)

Hypocalcemia (72.9%), hyperkalemia (48.6%) and hyponatremia (35.1%) were reported on day 1 of life. This is comparable to a study by Jitendra(26) on the prevalence of electrolyte disturbances on asphyxiated infants which found that infants with severe birth asphyxia had hypocalcemia, hyponatremia and hyperkalemia.

The incidence of hypocalcemia reduced from 72.9% before Therapeutic Hypothermia to 5.4% after TH, hyponatremia reduced from 35.1%% before TH to 0% after TH and hyperkalemia reduced from 48.6% before TH to 2.7% after TH. TH was associated with a lower incidence of hypocalcemia, hyponatremia and hyperkalemia.

In this study, Therapeutic hypothermia did not result in significant further derangements of sodium, calcium and potassium levels from baseline. A study by Prempunpong et al showed increased incidence of hypercalcemia following Therapeutic Hypothermia in neonates with HIE(29). Retrospective cohort study by Prempunpong(29) on the effect of therapeutic hypothermia on serum sodium levels, found that the incidence of hyponatremia increased from 48% before TH to 76% after TH.

The secondary objective involved comparison of electrolytes between the therapeutic hypothermia group and no therapeutic hypothermia group.

Hypocalcemia, hyperkalemia and hyponatremia were reported in both groups on day 1 of life. This is comparable to a study by Jitendra(26) on the prevalence of electrolyte disturbances on asphyxiated infants which found that infants with severe birth asphyxia had hypocalcemia,

hyponatremia and hyperkalemia. These electrolyte derangements are common in perinatal asphyxia and occur at baseline in both cooled and non-cooled neonates(12,22,30)

There was no statistically significant difference in calcium, sodium and potassium levels comparing the Therapeutic Hypothermia and non-Therapeutic Hypothermia group on day 2 of life (cooling phase). None of the five major RCTs on TH reported significant changes in serum calcium, sodium and potassium levels during cooling (33)

On day 4 of life (rewarming phase), there was no significant difference in sodium and potassium levels in the TH group compared to the non-TH group. However, the incidence of hypocalcemia was higher in the non-TH group (29.7%) compared to the TH group (5.4%). Here the difference between the two groups was statistically significant with a p value of 0.0043 and an odds ratio of 0.15 (95% Confidence Interval 0.01 – 0.94). This was similar to a study by Vayalthrikkovil(30) which found hypocalcemia in 12% of infants on TH compared to 21% in non TH infants post therapeutic Hypothermia. In a study by Prempunpong et al (29) the incidence of hypocalcemia was higher in the non-TH group , with a statistically significant difference on day 2 of life (18 vs 0%; p = 0.01) and in the TH group

5.1 STUDY STRENGTHS/LIMITATIONS

5.1.1 Strengths

Fluid and electrolyte supplementation may affect the electrolyte values therefore daily fluid and electrolyte intake was recorded for all participants and compared with the electrolyte values.

Study participants were matched by age weight and degree of HIE at enrolment to limit selection bias

5.2.2 Limitations

There were limited number of cooling devices thus only a limited number of infants were started on Therapeutic hypothermia thus the sample size was small

6.CONCLUSIONS AND RECOMMENDATIONS

6.1 CONCLUSIONS

- Therapeutic Hypothermia was not found to have further adverse derangements in sodium, potassium and calcium levels from baseline and has been associated with lower incidence of hypocalcemia, hyperkalemia and hyponatremia
- At baseline, both the Therapeutic Hypothermia and no Therapeutic Hypothermia groups had deranged serum electrolytes (hyperkalemia, hyponatremia and hypocalcemia). This indicates that Perinatal asphyxia causes derangements in these electrolytes.

6.2 RECOMMENDATIONS

- Therapeutic hypothermia resulted in lower incidence of hypocalcemia, hyponatremia and hyperkalemia. However, these derangements persisted in a significant number of subjects during the cooling and rewarming phases thus electrolyte levels should be monitored daily during Therapeutic Hypothermia to identify and correct any abnormalities
- All infants with moderate and severe HIE should have serum electrolytes monitored whether on Therapeutic Hypothermia or not

7. ETHICAL CONSIDERATIONS

The study was conducted after approval by the Kenyatta National Hospital and University of Nairobi (KNH/UON) Ethics and Research Committee (ERC). Written consent was obtained from parents/guardians after explanation of what the study entails. Beneficial treatment was not withheld and any electrolyte derangements were reported to the NBU team immediately for appropriate management. The investigator did not assign subjects into the respective groups. The subjects in the control group were infants who met the criteria for Therapeutic Hypothermia but did not receive the intervention due to the limited number of cooling devices available at KNH NBU.

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APPENDIX I: DEFINITION AND STAGING OF PERINATAL ASPHYXIA. (34)

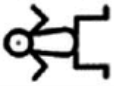
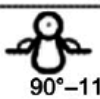
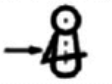
"Failure to initiate and sustain breathing at birth."[1] PLUS clinical evidence of hypoxic ischemic encephalopathy Sarnat and Sarnat stage 1, 2 or 3.

Sarnat and Sarnat Clinical Staging of Hypoxic Ischemic Encephalopathy.

Variable	Stage 1	Stage 2	Stage 3
Level of consciousness	Alert/Hyperalert	Lethargy	Coma
Muscle tone	Normal	Hypotonia	Flaccidity
Seizures	Absent	Focal/Multifocal	Generalized
Reflexes			
Suck	Active	Weak	Absent
Moro	Exaggerated	Incomplete	Absent
Grasp	Normal/Exaggerated	Weak	Absent

APPENDIX 2: NEW BALLARD SCORE FOR GESTATIONAL AGE ASSESSMENT(35)

Neuromuscular Maturity

Score	-1	0	1	2	3	4	5
Posture							
Square window (wrist)	 >90°	 90°	 60°	 45°	 30°	 0°	
Arm recoil		 180°	 140°–180°	 110°–140°	 90°–110°	 <90°	
Popliteal angle	 180°	 160°	 140°	 120°	 100°	 90°	 <90°
Scarf sign							
Heel to ear							

Physical Maturity

Skin	Sticky, friable, transparent	Gelatinous, red, translucent	Smooth, pink; visible veins	Superficial peeling and/or rash; few veins	Cracking, pale areas; rare veins	Parchment, deep cracking; no vessels	Leathery, cracked wrinkled
Lanugo	None	Sparse	Abundant	Thinning	Bald areas	Mostly bald	
Plantar surface	Heel-toe 40-50 mm: –1 <40 mm: –2	>50 mm, no crease	Faint red marks	Anterior transverse crease only	Creases anterior ⅔	Creases over entire sole	
Breast	Imperceptible	Barely perceptible	Flat areola, no bud	Stippled areola, 1–2 mm bud	Raised areola, 3–4 mm bud	Full areola, 5–10 mm bud	
Eye/Ear	Lids fused loosely: –1 tightly: –2	Lids open; pinna flat; stays folded	Slightly curved pinna; soft; slow recoil	Well curved pinna; soft but ready recoil	Formed and firm, instant recoil	Thick cartilage, ear stiff	
Genitals (male)	Scrotum flat, smooth	Scrotum empty, faint rugae	Testes in upper canal, rare rugae	Testes descending, few rugae	Testes down, good rugae	Testes pendulous, deep rugae	
Genitals (female)	Clitoris prominent, labia flat	Clitoris prominent, small labia minora	Clitoris prominent, enlarging minora	Majora and minora equally prominent	Majora large, minora small	Majora cover clitoris and minora	

Maturity Rating

Score	Weeks
-10	20
-5	22
0	24
5	26
10	28
15	30
20	32
25	34
30	36
35	38
40	40
45	42
50	44

APPENDIX 3:DATA COLLECTION TOO-L EFFECT OF THERAPEUTIC HYPOTHERMIA ON SERUM ELECTROLYTES IN NEONATES WITH MODERATE TO SEVERE HYPOXIC ISCHEMIC ENCEPHALOPATHY AT KENYATTA NATIONAL HOSPITAL

Abbreviated name		Date of Enrollment	
Study Number		Time of enrollment	

Neonate Biodata

Gestational age (LNMP)		Gestational age (Finnstrom)	
Date of birth - ___/___/___ ___: ___am/pm		Date of admission- ___/___/___ ___: ___am/pm	
Sex M / F		Place of Delivery-KNH/Referral	
Mode of delivery-SVD/CS	Weight gms – Birth____, Day 1____, Day 2_____, Day 3_____, Day 4_____		
Intubated/Mech Ven Y/N	APGAR (1 min-__ /5 min -__ /10 min -__)		Sarnat Stage
Resp rate-Day 1……2……..4……		HR-Day 1….2…..4……	HR-Day 4
Fluid intake-Day 1(mls) Total-	EBM __ml D10 __ml NS __ ml KCL __ml	Fluid intake-Day 2(mls) Total-	EBM __ml D10 __ml NS __ ml KCL __ml
Fluid intake-Day 3(mls) Total-	EBM __ml D10 __ml NS __ ml KCL __ml	Fluid intake-Day 4(mls) Total-	EBM __ml D10 __ml NS __ ml KCL __ml
Urine output-Day 1(mls)		Urine output-Day 2(mls)	
Urine output-Day 3(mls)		Urine output-Day 4(mls)	

Maternal Biodata

Age-	Number of ANC-	Occupation	Parity
Maternal Status at Enrollment-Stable/Critical/Dead		Marital status- Single/ Married/Divorced	
Duration of Labour-	Duration of DOL-	Hx HTN Y/N	Hx of endocrine dx Y/N

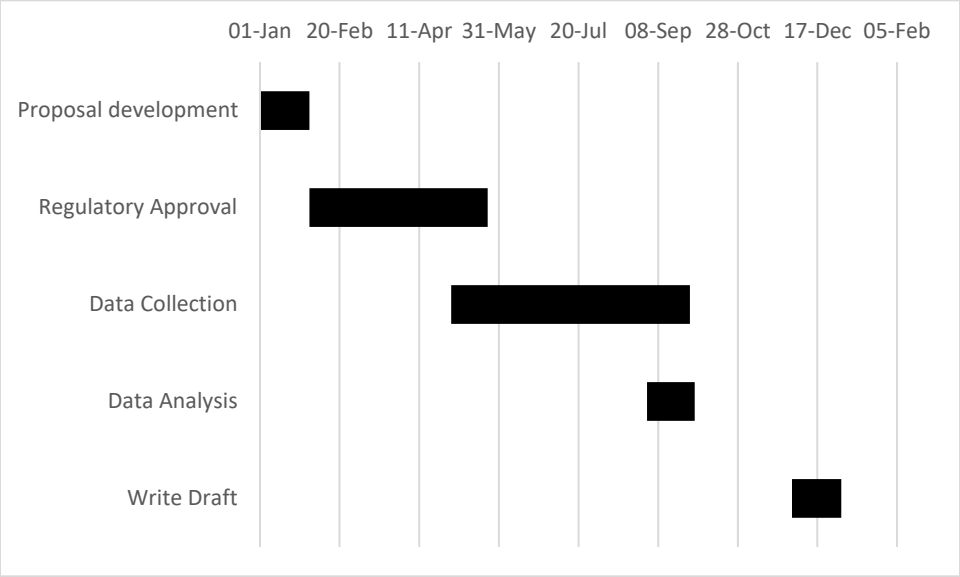
Neonate Laboratory Results

Electrolyte	Value	Date/ Time of sample removal	Date/Time of sample processing
Calcium- Day 1		___/___/___ ___: ___am/pm	___/___/___ ___: ___am/pm
Calcium- Day 2		___/___/___ ___: ___am/pm	___/___/___ ___: ___am/pm
Calcium- Day 4		___/___/___ ___: ___am/pm	___/___/___ ___: ___am/pm
Sodium- Day 1		___/___/___ ___: ___am/pm	___/___/___ ___: ___am/pm
Sodium- Day 2		___/___/___ ___: ___am/pm	___/___/___ ___: ___am/pm
Sodium- Day 4		___/___/___ ___: ___am/pm	___/___/___ ___: ___am/pm
Potassium- Day 1		___/___/___ ___: ___am/pm	___/___/___ ___: ___am/pm
Potassium-Day 2		___/___/___ ___: ___am/pm	___/___/___ ___: ___am/pm

Potassium-Day 4		___/___/___ ___: ___am/pm	___/___/___ ___: ___am/pm

Data Entry by:

APPENDIX 4. GANTT CHART



APPENDIX 5: STUDY BUDGET

Proposal development	**Item** Printing Questionnaires Proposal copies KNH-UON ERC Research Assistants 2 Persons Laboratory investigations Sodium/Potassium 450 per test x3 tests per infant for 74 infants Calcium 300 per test x3 tests per infant for 74 infants Stationary Statistician Printing drafts Printing thesis	**Amount (KES)** 10000 6000 2000 30000 99000 66000 2500 30000 5000 6000
	Contingency	30000
	Total	**280000**

APPENDIX 6: STANDARD OPERATING PROCEDURES FOR ELECTROLYTE ANALYSIS

Newborns that satisfy the inclusion criteria will be enrolled into the study until the sample size is achieved. Written informed consent will be obtained from parents/guardians.

For the therapeutic hypothermia group, samples for serum calcium, sodium and potassium will be collected on day 1, day 2 of life (maintenance phase) and day 4 of life (rewarming phase).

For the non-therapeutic hypothermia group samples will be collected on day1, 2 and 4 of life. 1ml of blood will be collected into a vacutainer via venipuncture of the cubital vein. Results will be recorded in a questionnaire.

Infection prevention measures will be instituted including those of COVID 19. All the samples will be collected by the principal investigator and a qualified research assistant trained by the principal investigator. Samples will be collected as 1mls in a Red-top tube. The sample and request forms will be filled using double identifiers, date and time of collection. The samples will be delivered to the Biochemistry laboratory within 30 minutes of extraction. Specimen will be received in the lab by a health records officer and assigned a lab number. The specimen will be centrifuged and serum obtained. Serum will be analysed in the HUMASTAR 600 machine which is fully automated. The machine has internal quality control checks done daily by laboratory personnel. External quality control is done every 2 months by the Human Quality Assessment Service. The test results will be picked from the laboratory, the information counterchecked with the subject data before being entered into the spreadsheet. In the case of any abnormal values, the researcher or her assistant will immediately inform the clinical team for review and timely intervention.

Rejected samples will be noted and recollected within in the stipulated time period.

APPENDIX 7: CONSENT FORM- THERAPEUTIC HYPOTHERMIA GROUP

<table>
<tr><td>TITLE</td><td colspan="5">EFFECT OF THERAPEUTIC HYPOTHERMIA ON SERUM ELECTROLYTES IN NEONATES WITH MODERATE TO SEVERE HYPOXIC ISCHEMIC ENCEPHALOPATHY AT KENYATTA NATIONAL HOSPITAL</td></tr>
<tr><td>SCOPE</td><td colspan="5">Study participants</td></tr>
<tr><td>SERIAL NUMBER</td><td></td><td>DATE</td><td></td><td>SITE</td><td>KNH
NBU</td></tr>
</table>

This Informed Consent Form has two parts:

1. Information sheet- To share information with you
2. Consent form- If you choose to participate

Part 1: Information Sheet

Introduction This is a study to determine the effect of therapeutic hypothermia on serum electrolytes in neonates with HIE at the Kenyatta National Hospital Newborn Unit.

Purpose of the study: The study primarily aims to determine the effect of therapeutic hypothermia on serum electrolytes in infants with HIE at Kenyatta National Hospital NBU.

Procedures: You will be provided with a questionnaire.

Blood samples will be collected on your baby on day 1, 2 and day 4 of life. These blood samples are collected routinely, daily on babies undergoing therapeutic hypothermia at KNH NBU.

Benefits: The findings of this study will help to improve the quality of care offered to patients undergoing therapeutic hypothermia at the KNH NBU by allowing us to study the electrolyte changes associated with Therapeutic Hypothermia

Risks: There will be minimal risk to your baby during this study. There will be mild pain and discomfort during blood sampling

Confidentiality: The finding so this study will not be shared with anyone other than the researchers and the NBU team involved in the care and management of your baby.

Your participation in this study is voluntary. Should you wish to not participate, you are free to do so.

Who to contact:

Investigator: Dr. Angeline Sambasi

Tel 0723680434 Email: asambasi@students.uonbi.ac.ke

Address- 12399-20100 Nakuru Kenya

Supervisors:

Aggrey Wasunna

Professor of Neonatal Medicine and Paediatrics,

School of Medicine, University of Nairobi

Address-25700 Lavington 00603 Nairobi

wasunnabill@gmail.com

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Dr Ombaba Osano, Lecturer, Paediatric Cardiologist

Department of Paediatrics and Child Health, University of Nairobi

bosano@uonbi.ac.ke

+254722646720

The Ethics and Research Committee, Kenyatta National Hospital/University of Nairobi (KNH/UON ERC) has approved this study.

Contacts:

The Chairman,

Kenyatta National Hospital/University of Nairobi Ethics and Research Committee

P.O.BOX 20723

Nairobi, Kenya.

Email: uonknh_erc@uonbi.ac.ke
Telephone: 0799-495829 / 0799-495830

Part II: Certificate of consent.

I, being the parent/guardian of _____ (name of baby) have had the details of this research explained to me. I have understood the procedures, benefits and risks of this study, and that my participation is voluntary and I can withdraw my baby from this study, at any time, if I wish to.

Name of Parent/guardian_____

Signature or thumb print of Parent/guardian_____

Date _____ Day/month/year

FOMU YA RIDHAA- TIBA HYPOTHERMIA

Utangulizi: Huu ni utafiti wa kubainisha athari za hypothermia ya matibabu kwa elektroliti za seramu kwa watoto wachanga walio na HIE katika Kitengo cha Watoto Wachanga cha Hospitali ya Kitaifa ya Kenyatta.

Madhumuni ya utafiti: Utafiti unalenga kubainisha athari za hypothermia ya matibabu kwenye elektroliti za seramu kwa watoto wachanga walio na HIE katika Hospitali ya Kitaifa ya Kenyatta NBU.

Taratibu: Utapewa dodoso.

Sampuli za damu zitakusanywa kwa mtoto wako siku ya 1,2 na siku ya 4 ya maisha. Sampuli hizi za damu hukusanywa kwa utaratibu, kila siku kwa watoto wanaopata hypothermia ya matibabu kat katika KNH NBU.

Manufaa: Matokeo ya utafiti huu yatasaidia kuboresha ubora wa huduma inayotolewa kwa wagonjwa wanaopitia hypothermia ya matibabu katika KNH NBU kwa kuturuhusu kujifunza mabadiliko ya elektroliti yanayohusiana na Hypothermia ya Tiba.

Hatari: Hakutakuwa na hatari kwako au kwa mtoto wako wakati wa utafiti huu.

Usiri: Matokeo ya utafiti huu hayatashirikiwa na mtu yeyote isipokuwa watafiti na timu ya NBU inayohusika katika utunzaji na usimamizi wa mtoto wako.

Kushiriki kwako katika utafiti huu ni kwa hiari. Ikiwa ungependa kutoshiriki, uko huru kufanya hivyo.

Mawasiliano:

Mpelelezi: Dk Angeline Sambasi
Tel 0723680434 Email: asambasi@students.uonbi.ac.ke
Anwani- 12399-20100 Nakuru Kenya

Wasimamizi:

Aggrey Wasunna
Profesa wa Tiba ya Watoto wachanga na Madaktari wa Watoto,
Shule ya Tiba, Chuo Kikuu cha Nairobi
Anwani-25700 Lavington 00603 Nairobi
wasunnabill@gmail.com
+254722700444

Dk Ombaba Osano, Mhadhiri, Daktari Bingwa wa Magonjwa ya Moyo kwa Watoto
Idara ya Madaktari wa Watoto na Afya ya Mtoto, Chuo Kikuu cha Nairobi
bosano@uonbi.ac.ke
+254722646720

Kamati ya Maadili na Utafiti, Hospitali ya Kitaifa ya Kenyatta/Chuo Kikuu cha Nairobi (KNH/UON ERC) imeidhinisha utafiti huu.

Anwani:

Mwenyekiti,

Hospitali ya Kitaifa ya Kenyatta/Kamati ya Maadili na Utafiti ya Chuo Kikuu cha Nairobi

P.O.BOX 20723

Nairobi, Kenya.

Barua pepe: uonknh_erc@uonbi.ac.ke
Tel: 0799-495829 / 0799-495830

Sehemu ya II: Cheti cha idhini.

Mimi, nikiwa mzazi/mlezi wa _____ (jina la mtoto) nimefafanuliwa maelezo ya utafiti huu. Nimeelewa taratibu, manufaa na hatari za utafiti huu, na kwamba ushiriki wangu ni wa hiari na ninaweza kumtoa mtoto wangu kutoka kwa utafiti huu, wakati wowote, nikipenda.

Jina la Mzazi/mlezi_____

Sahihi au alama ya kidole gumba cha Mzazi/mlezi_____

Tarehe _____ Siku/mwezi/mwaka

APPENDIX 8: CONSENT FORM- CONTROL GROUP

TITLE	**EFFECT OF THERAPEUTIC HYPOTHERMIA ON SERUM ELECTROLYTES IN NEONATES WITH MODERATE TO SEVERE HYPOXIC ISCHEMIC ENCEPHALOPATHY AT KENYATTA NATIONAL HOSPITAL**				
SCOPE	Study participants				
SERIAL NUMBER		DATE		SITE	KNH NBU

Investigator: Dr. Angeline Sambasi

Tel 0723680434 Email: asambasi@students.uonbi.ac.ke

Address- 12399-20100 Nakuru Kenya

This Informed Consent Form has two parts:

3. Information sheet- To share information with you
4. Consent form- If you choose to participate

Part 1: Information Sheet

Introduction This is a study to determine the effect of therapeutic hypothermia on serum electrolytes in neonates with HIE at the Kenyatta National Hospital Newborn Unit.

Purpose of the study: The study primarily aims to determine the effect of therapeutic hypothermia on serum electrolytes in infants with HIE at Kenyatta National Hospital NBU.

Procedures: You will be provided with a questionnaire.

Blood samples will be collected on your baby on day 1, 2 and 4 of life. These blood samples are collected routinely, daily on babies with HIE at KNH NBU.

Benefits: The findings of this study will help to improve the quality of care offered to patients undergoing therapeutic hypothermia at the KNH NBU.

Risks: There will be minimal risk to your baby during this study. There will be mild pain and discomfort during blood sampling

Confidentiality: The finding so this study will not be shared with anyone other than the researchers and the NBU team involved in the care and management of your baby.

Your participation in this study is voluntary. Should you wish to not participate, you are free not to do so.

Who to contact:

Investigator: Dr. Angeline Sambasi

Tel 0723680434 Email: asambasi@students.uonbi.ac.ke

Address- 12399-20100 Nakuru Kenya

Supervisors:

Aggrey Wasunna

Professor of Neonatal Medicine and Paediatrics,

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Dr Ombaba Osano, Lecturer, Paediatric Cardiologist

Department of Paediatrics and Child Health, University of Nairobi

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+254722646720

The Ethics and Research Committee, Kenyatta National Hospital/University of Nairobi (KNH/UON ERC) has approved this study.

Contacts:

The Chairman,

Kenyatta National Hospital/University of Nairobi Ethics and Research Committee

P.O.BOX 20723

Nairobi, Kenya.

Email: uonknh_erc@uonbi.ac.ke
Telephone: 0799-495829 / 0799-495830

Part II: Certificate of consent.

I, being the parent/guardian of _____ (name of baby) have had the details of this research explained to me. I have understood the procedures, benefits and risks of this study, and that my participation is voluntary and I can withdraw my baby from this study, at any time, if I wish to.

Name of Parent/guardian_____

Signature of Parent/guardian_____

Date _____ Day/month/year

FOMU YA RIDHAA- KIKUNDI CHA KUDHIBITI

Utangulizi: Huu ni utafiti wa kubainisha athari za hypothermia ya matibabu kwa elektroliti za seramu kwa watoto wachanga walio na HIE katika Kitengo cha Watoto Wachanga cha Hospitali ya Kitaifa ya Kenyatta.

Madhumuni ya utafiti: Utafiti unalenga kubainisha athari za hypothermia ya matibabu kwenye elektroliti za seramu kwa watoto wachanga walio na HIE katika Hospitali ya Kitaifa ya Kenyatta NBU.

Taratibu: Utapewa dodoso.

Sampuli za damu zitakusanywa kwa mtoto wako siku ya 1, 2 na 4 ya maisha. Sampuli hizi za damu hukusanywa kwa utaratibu, kila siku kwa watoto walio na HIE katika KNH NBU.

Manufaa: Matokeo ya utafiti huu yatasaidia kuboresha ubora wa huduma inayotolewa kwa wagonjwa wanaopitia hypothermia ya matibabu katika KNH NBU kwa kuturuhusu kujifunza mabadiliko ya elektroliti yanayohusiana na Hypothermia ya Tiba.

Hatari: Hakutakuwa na hatari kwako au kwa mtoto wako wakati wa utafiti huu.

Usiri: Matokeo ya utafiti huu hayatashirikiwa na mtu yeyote isipokuwa watafiti na timu ya NBU inayohusika katika utunzaji na usimamizi wa mtoto wako.

Kushiriki kwako katika utafiti huu ni kwa hiari. Ikiwa ungependa kutoshiriki, uko huru kufanya hivyo.

Mawasiliano:

Mpelelezi: Dk Angeline Sambasi
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Wasimamizi:

Aggrey Wasunna
Profesa wa Tiba ya Watoto wachanga na Madaktari wa Watoto,
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Kamati ya Maadili na Utafiti, Hospitali ya Kitaifa ya Kenyatta/Chuo Kikuu cha Nairobi (KNH/UON ERC) imeidhinisha utafiti huu.

Anwani:

Mwenyekiti,

Hospitali ya Kitaifa ya Kenyatta/Kamati ya Maadili na Utafiti ya Chuo Kikuu cha Nairobi

P.O.BOX 20723

Nairobi, Kenya.

Barua pepe: uonknh_erc@uonbi.ac.ke
Tel: 0799-495829 / 0799-495830

Sehemu ya II: Cheti cha idhini.

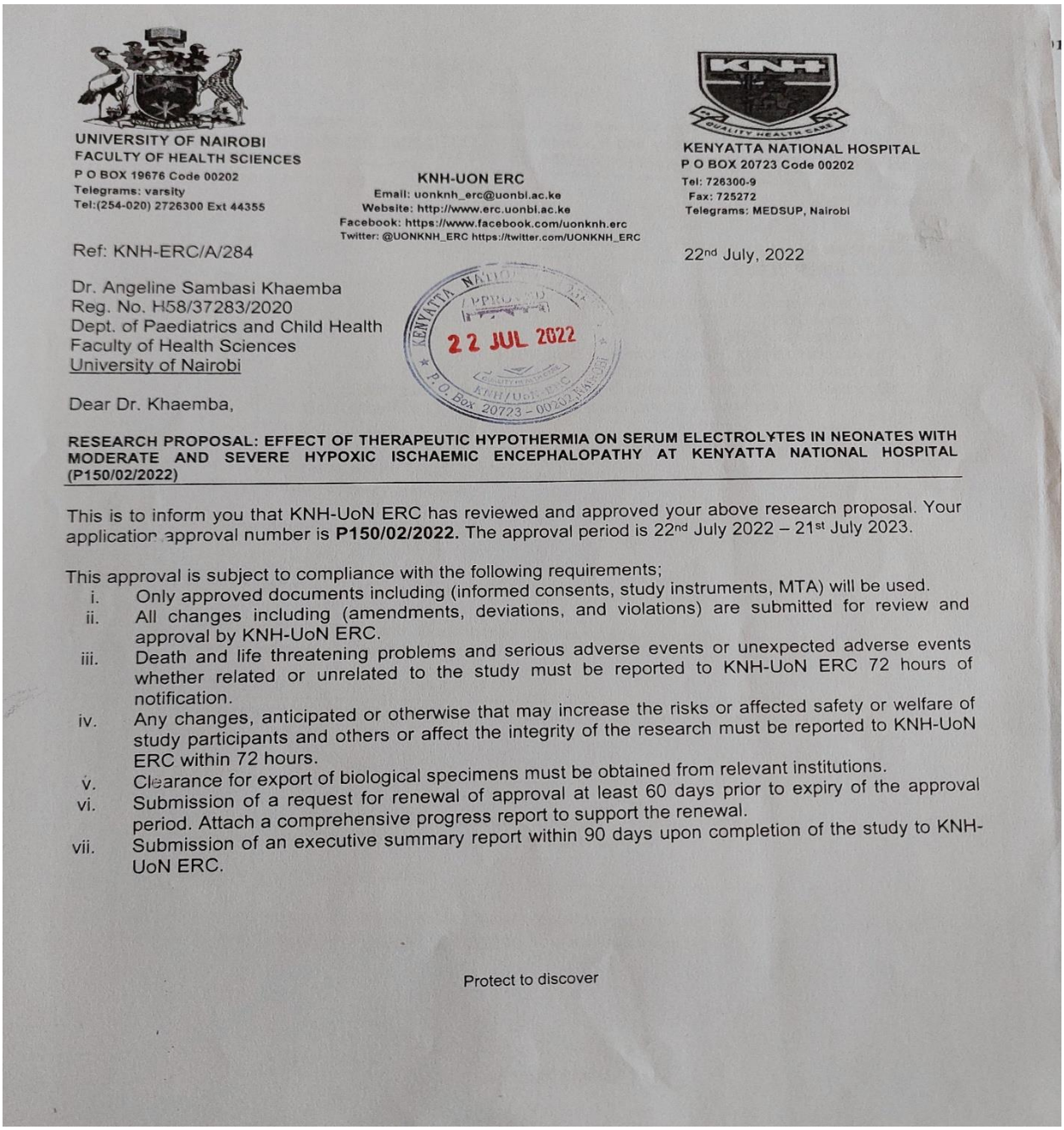
Mimi, nikiwa mzazi/mlezi wa _____ (jina la mtoto) nimefafanuliwa maelezo ya utafiti huu. Nimeelewa taratibu, manufaa na hatari za utafiti huu, na kwamba ushiriki wangu ni wa hiari na ninaweza kumtoa mtoto wangu kutoka kwa utafiti huu, wakati wowote, nikipenda.

Jina la Mzazi/mlezi_____

Sahihi au alama ya kidole gumba cha Mzazi/mlezi_____

Tarehe _____ Siku/mwezi/mwaka

APPENDIX 9: LETTER OF APPROVAL FROM KNH-UON/ERC



UNIVERSITY OF NAIROBI
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KNH-UON ERC
Email: uonknh_erc@uonbi.ac.ke
Website: http://www.erc.uonbi.ac.ke
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KENYATTA NATIONAL HOSPITAL
P O BOX 20723 Code 00202
Tel: 726300-9
Fax: 725272
Telegrams: MEDSUP, Nairobi

Ref: KNH-ERC/A/284

22nd July, 2022

Dr. Angeline Sambasi Khaemba
Reg. No. H58/37283/2020
Dept. of Paediatrics and Child Health
Faculty of Health Sciences
University of Nairobi

KENYATTA NATIONAL HOSPITAL APPROVED 22 JUL 2022 KNH/UoN-ERC P.O. Box 20723 - 00202 NAIROBI

Dear Dr. Khaemba,

RESEARCH PROPOSAL: EFFECT OF THERAPEUTIC HYPOTHERMIA ON SERUM ELECTROLYTES IN NEONATES WITH MODERATE AND SEVERE HYPOXIC ISCHAEMIC ENCEPHALOPATHY AT KENYATTA NATIONAL HOSPITAL (P150/02/2022)

This is to inform you that KNH-UoN ERC has reviewed and approved your above research proposal. Your application approval number is **P150/02/2022.** The approval period is 22nd July 2022 – 21st July 2023.

This approval is subject to compliance with the following requirements;

i. Only approved documents including (informed consents, study instruments, MTA) will be used.
ii. All changes including (amendments, deviations, and violations) are submitted for review and approval by KNH-UoN ERC.
iii. Death and life threatening problems and serious adverse events or unexpected adverse events whether related or unrelated to the study must be reported to KNH-UoN ERC 72 hours of notification.
iv. Any changes, anticipated or otherwise that may increase the risks or affected safety or welfare of study participants and others or affect the integrity of the research must be reported to KNH-UoN ERC within 72 hours.
v. Clearance for export of biological specimens must be obtained from relevant institutions.
vi. Submission of a request for renewal of approval at least 60 days prior to expiry of the approval period. Attach a comprehensive progress report to support the renewal.
vii. Submission of an executive summary report within 90 days upon completion of the study to KNH-UoN ERC.

Protect to discover

Prior to commencing your study, you will be expected to obtain a research license from National Commission for Science, Technology and Innovation (NACOSTI) https://research-portal.nacosti.go.ke and also obtain other clearances needed.

Yours sincerely,

DR. BEATRICE K.M. AMUGUNE
SECRETARY, KNH-UoN ERC

c.c. The Dean, Faculty of Health Sciences, UoN
The Senior Director, CS, KNH
The Chairperson, KNH- UoN ERC
The Assistant Director, Health Information Dept., KNH
The Chair, Dept. of Paediatrics and Child Health, UoN
Supervisors: Prof. Aggrey Wasunna, Dept. of Paediatrics and Child Health, UoN
Dr. Boniface O. Osano, Dept. of Paediatrics and Child Health, UoN

SERUM ELECTROLYTES IN NEONATES WITH MODERATE AND SEVERE HYPOXIC ISCHAEMIC ENCEPHALOPATHY ON THERAPEUTIC HYPOTHERMIA AT KENYATTA NATIONAL HOSPITAL

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