COAGULOPATHY AND THROMBOCYTOPENIA IN ASPHYXIATED NEONATES UNDERGOING THERAPEUTIC HYPOTHERMIA IN KENYATTA NATIONAL HOSPITAL NEW BORN UNIT

A dissertation submitted in partial fulfillment of Masters of Medicine (M.Med) in Paediatrics and Child Health.

University of Nairobi

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MMED PAEDIATRICS AND CHILD HEALTH

Student's declaration

This dissertation proposal is my original work and has not been presented for the award of a degree in any other university.

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Signed: ..... Date: 10th November 2021

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Dedication

With so much love and respect, I dedicate this book to my beloved partner Fred. Your constant support, encouragement, resilience and love have been an impetus to this successful journey.

Acknowledgement to my supervisors, Professor Wasunna and Dr. Owino for their time and rich contribution to this work; and to my partner and statistician Dr. Fredrick Mutisya for the data analysis. To God be the glory.

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List of abbreviations

aPTT -	Activated Partial Thromboplastin Time
ATP -	Adenosine Triphosphate
Ca^{2+} -	Calcium
HIE -	Hypoxic – Ischaemic Encephalopathy
INR -	International Normalised Ratio
KDHS -	Kenya Demographic and Health Survey
K^{+} -	Potassium
KA -	Kainate
KNH -	Kenyatta National Hospital
Na^{+}-	Sodium
Na^{+}/K^{+} ATPase -	Sodium, Potassium ATPase pump
NBU -	New Born Unit
NMDA -	N-methyl-D-aspartate
TH -	Therapeutic hypothermia
WHO -	World Health Organisation
SVD -	Spontaneous Vertex Delivery
CS -	Caesarian Section

Definition of terms

1. **Term Neonate**

   A new born infant delivered at or after 37 completed weeks of gestation and is in the first 28 days of life.

2. **Perinatal Asphyxia**

   "Failure to initiate and sustain breathing at birth" (1) plus clinical evidence of Hypoxic Ischemic Encephalopathy as defined by Sarnat and Sarnat staging.(2)

3. **HIE**

   Acute non-static encephalopathy or brain injury caused by intrapartum or late antepartum brain hypoxia and ischemia.

4. **Coagulopathy**

   Derangement in INR > 1.2 (3)

   Derangement in aPTT > 35sec (3)

5. **Thrombocytopenia –** Platelet count of < 150 x 10^9 /L (3)

6. **Uremia –** Urea >8.2mmol/L (3)

Abstract

Introduction:

Globally, nine million new cases of perinatal asphyxia are reported annually and this contributes to 38% of the under-5 mortality. In Kenya, approximately 31.6% of neonatal mortality is attributed to perinatal asphyxia. Additionally, perinatal asphyxia leads to long term neurological sequalae such as delayed milestones and cerebral palsy. Currently, the standard care for neonates with moderate and severe perinatal asphyxia, in addition to supportive care, is Therapeutic Hypothermia (TH) to prevent long term neurologic sequalae. TH is achieved using either whole body or selective head cooling. TH using the MiraCradle™ is regularly used at KNH NBU to manage neonates who meet the treatment criteria. The MiraCradle™ is based on Phase Change Material to achieve a steady rectal temperature of between 33-34^0 C (target: 33.5^0 C) for 72 hours to effect whole body cooling. Despite being reported to have consistent efficacy in reduction of mortality and neurodevelopmental disability, TH has potential negative effects on coagulation system and platelet counts and this should be monitored during therapy.

Objectives

To determine the effect of therapeutic hypothermia on coagulation profile and platelet counts in neonates with moderate and severe perinatal asphyxia compared to those not on TH.

Methodology

This was a prospective cohort study among term neonates with moderate and severe asphyxia admitted to the KNH NBU. The first cohort had 30 neonates who met criteria to undergo TH in KNH NBU and were cooled in addition to the standard supportive care. The second cohort were 33 age, birth weight and degree of HIE matched term neonates who met criteria for TH but were not cooled due to the limited availability of the required equipment and were given the standard supportive care only. Consecutive sampling of both groups fulfilling the criteria was done until the desired number was achieved. Informed consent was obtained from caregiver of eligible patients. Laboratory tests were done on day one and day three of treatment.

Data analysis

Data was presented in tables and analysed using STATAv12.0. Relevant descriptive statistics were used to summarise the data. Between and within group analysis was done for group comparative analysis.

Ethical Consideration

The investigator did not randomize patients into the respective groups. Patients on TH received the treatment on a first come first served basis. Any patient who met criteria for TH but missed due to limited number of cooling devices was enrolled into the comparative group.

Results

The total study size was 63 with 30 undergoing TH and 33 not on TH. Vitamin K administration was noted to be suboptimal in both groups (57% receiving vitamin K at birth in the TH group and only 18% in the comparative group). The baseline median INR for both groups was noted to be above the cut off of 1.2, with TH group having a baseline median INR of 1.37 (IQR 0.57) and comparative group having a baseline median INR of 1.53 (IQR 0.48). The baseline median aPTT for both groups was noted to be above the cut off of 35, with TH group having a baseline median aPTT of 36.7 (IQR 14.3) and comparative group having a baseline median aPTT of 37.5 (IQR 7.9). Baseline platelet counts in both groups were within the normal ranges of 150 - 450 x 10^9. In the TH group, the means and medians of day 1 and day 3 laboratory results for INR, aPTT, platelets, urea were compared. Of the four parameters, only platelet count showed a statistically significant drop with a mean difference of -35.63 x 10^9 p = < 0. 005. However, the drop in platelet count was not clinically significant since the counts did not go below 150 x 10^9. No factors were found to be significantly associated with the drop in platelet counts in the TH group.

Conclusion

With regards to coagulation function and platelet count, TH has not demonstrated adverse derangements in the parameters. In the study, both groups had elevated INR and aPTT values at baseline, indicating that asphyxia as an independent variable causes derangements in INR and aPTT.

Recommendation

Monitoring of platelet counts and coagulation function should be done for all neonates with moderate and severe hypoxic ischemic encephalopathy whether they are initiated on TH or not. Vitamin K administration should be implemented for all neonates admitted as per the essential newborn care protocol.

1 Introduction and literature review

1.1 Background

Perinatal asphyxia is defined by the WHO as "Failure to initiate and sustain breathing at birth." It is a condition that stems from compromised circulation and/or gaseous exchange to the fetus in the peripartum period resulting in hypoxemia and hypercapnia (1).Due to the presence of an oxygen debt in the tissues, metabolism switches from aerobic to anaerobic with resultant metabolic acidosis and profound systemic and neurologic sequelae in the affected fetus (4,5).

Asphyxia, as per the American Academy of Pediatrics (AAP) and the American College of Obstetrics and Gynecology (ACOG) guidelines, is diagnosed when the following criteria is met:

i. Profound metabolic or mixed academia (pH<7.00) in umbilical artery blood
ii. Persistence of APGAR score of 0-3 for longer than 5 minutes
iii. Neonatal neurologic sequelae (e.g. seizures, coma, hypotonia)
iv. Multiple organ involvement (e.g. kidneys, lungs, liver, heart and intestines) (6).

In 2008, an estimated 40% of all under five deaths was in the neonatal period and asphyxia accounted for 9% of these deaths (7). In Kenya, perinatal asphyxia accounts for up to 31.6% of neonatal mortality according to the Kenya Demographic Health Survey (KDHS) 2014 (8). In Kenyatta National Hospital New Born Unit, 20% of the weekly admissions is attributed to perinatal asphyxia and the documented mortality rate of these neonates is 31.1% by day 7 of life (9).

Perinatal asphyxia is associated with numerous multiorgan effects and its impact on the brain, resulting in hypoxic ischemic encephalopathy (HIE) is one of the grave complications linked to unfavorable outcomes (10). HIE is defined as "an acute non-static encephalopathy caused by intrapartum or late antepartum brain hypoxia and ischemia" (11).The Sarnat and Sarnat grading system is used to classify HIE into three categories which is predictive of neurodevelopmental disability in newborns with perinatal asphyxia (2).

The pathogenesis of neuronal damage in HIE is due to deprivation of oxygen and energy in the form of glucose which results in an abnormal and toxic biochemical neuronal milieu that causes cell damage and death (12).

This initial insult in HIE , termed as primary energy failure, results from oxygen deficiency leading to anaerobic metabolism and accumulation of lactate (13). Lactate accumulation is initially instrumental as an alternate source of energy but has detrimental impact by causing an impairment in cardiovascular autoregulation capacity which worsens an already compromised circulation (13).

With hypoxia, there is reduced oxidative phosphorylation and decreased production of adenosine triphosphate (ATP). ATP depletion leads to failure of transcellular ATP dependent Na^+/K^+ ATPase pump and an influx of extracellular electrolytes (Na^+) into the intracellular compartment with passive diffusion of water intracellularly resulting cell swelling, cell lysis and cell death by necrosis (cytotoxic edema) (14). Influx of Na^+ results in membrane depolarization and release of glutamate, an excitatory amino acid, into the synaptic cleft and reduced uptake by the post synaptic neuron (15).

Excessive release of glutamate triggers an excitotoxic cascade acting on 3 major ionotropic receptors: N-methyl-D-aspartate (NMDA) receptors, kainate receptors (KA) and alpha-amino-hydroxy-5-methyl-4-isoxazole propionic acid (AMPA) receptors. Activation of NMDA receptors leads to activation and opening of voltage gated Ca^{2+} channels (16). NMDA activation and intracellular calcium accumulation causes secondary cell death via activation of lipases, proteases, caspases, endonucleases and nitric oxide synthase (15). This mechanism leads to cell death by apoptosis (17).

The time period between primary and secondary energy failure is called the “latent phase”. This phase corresponds to the period when intervention can be implemented to reduce further neuronal injury (**Therapeutic Window**). This duration is reported to be optimally within the first 6 hours but lasts up to 24 hours (18).

Therapeutic Hypothermia confers neuronal protection by influencing molecular and cellular functions. A one degree decrease in body temperature results in approximately 6-10% reduction in cerebral oxygen consumption (19). Hypothermia also decreases neurotoxicity by reducing the influx of calcium into the neurons (20).

TH has demonstrated significant attenuation of the permeability of the blood brain barrier that is caused by ischemic insult which increases vascular permeability and edema (21).

Although hypothermia cannot completely eradicate production of toxic oxygen and nitrogen species, it markedly suppresses the levels of free radical production allowing action of endogenous antioxidants in reducing oxidative stress (22).

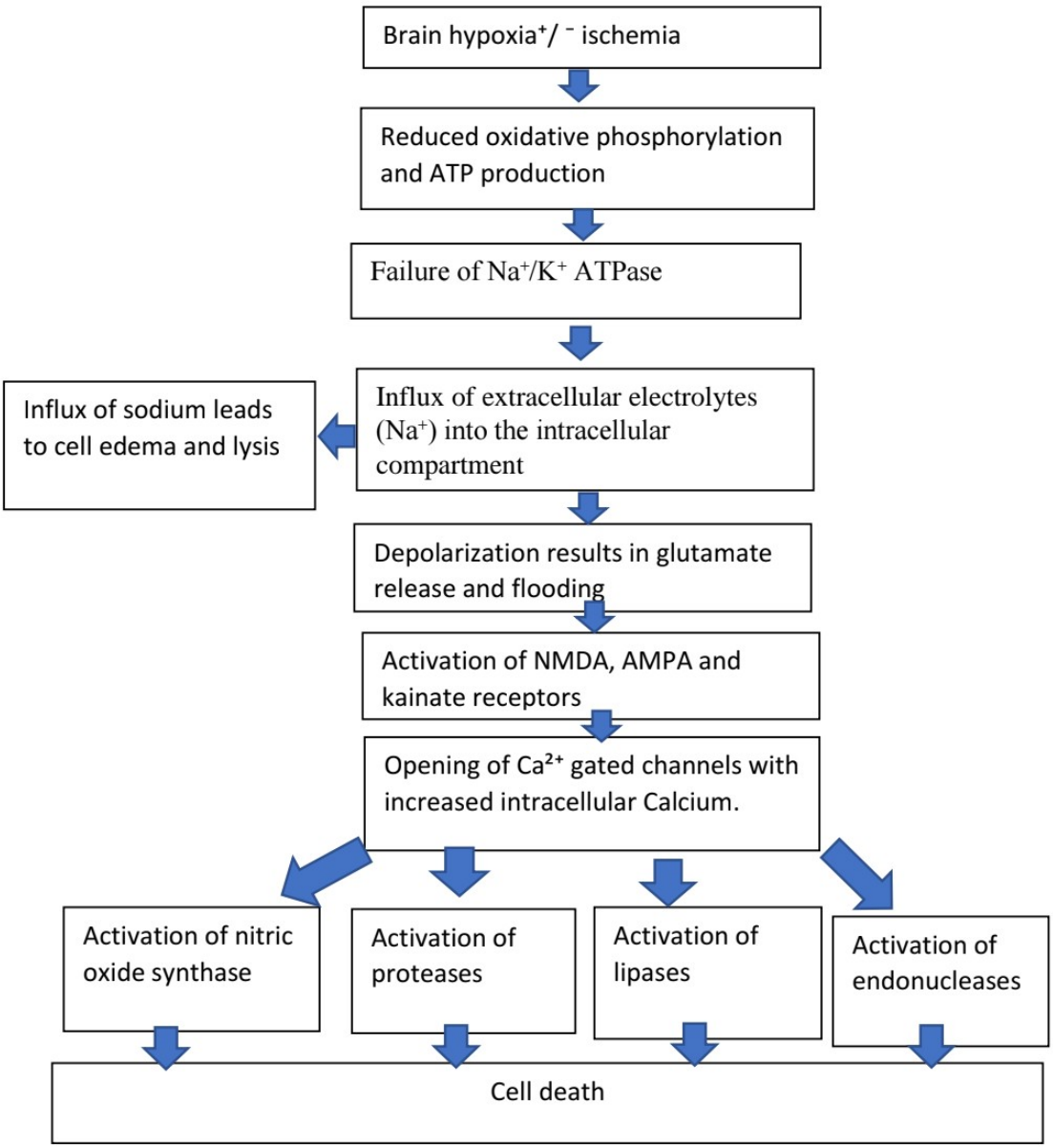


Figure 1: Schematic Illustration of the Pathophysiology of HIE

1.2 Literature review

1.2.1 Mechanism of neuroprotection with therapeutic hypothermia.

Hypoxic ischemic encephalopathy is marked by hypoxia, reduced levels of glucose and energy in form of ATP. When body temperatures are dropped, cerebral demand for oxygen declines hence conserving energy stores and phosphate. This in turn limits anaerobic glycolysis, lactate production and metabolic acidosis (23). Cerebral temperature, circulation and oxygen consumption(metabolism) have a linear relationship as demonstrated by Rosomoff and Holaday (24) in the figure below.

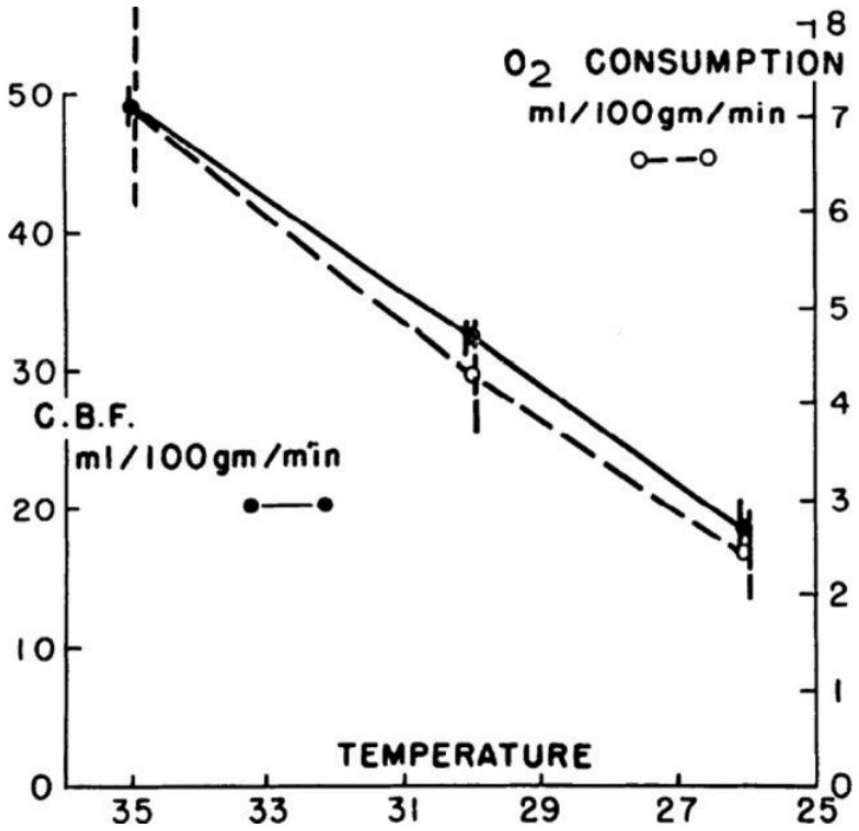


Figure 2: Relationship between Cerebral temperature, circulation and oxygen consumption(metabolism)

Solid circles joined by solid lines represent mean cerebral blood flows of 4 animals at 35°C, 30°C, and 26°C. Open circles joined by broken lines represent mean cerebral O_2 consumption of the same animals. (Reprinted from Rosomoff HL, Holaday DA,[9] with permission from the American Physiological Society.)

In the acute phase, there is reduced cerebral temperatures, cerebral perfusion and metabolism reduces, indicating conservation of cerebrovascular autoregulation (25). With cerebral ischemia, hypoxia, reduced levels of ATP and dysfunction of the Na^+/K^+ ATPase channels, membrane depolarization occurs causing excitotoxicity (15,16). Evidence from studies show that TH reduces the release of glutamate (26), prevents NMDA receptor activation (27) and reduces nitric oxide synthesis (28).

The subacute phase is marked by increased production of oxygen radicals and inflammation with damage to the blood brain barrier (21,29). Cell death in this phase is attributed to mitochondrial damage and release of regulatory proteins such as caspase 3 which regulate the apoptotic pathway (30). Therapeutic Hypothermia suppresses the release of regulatory proteins favoring the apoptotic pathway and increases activation of antiapoptotic pathways including increased expression of P53 which enhances neuronal repair (31).

1.2.2 Physiology of the clotting and coagulation system

Maintenance of hemostasis depends on concerted interaction between the vascular wall, platelets and coagulation proteins(32). When a blood vessel is injured, the smooth muscle wall of the vessel contracts and undergoes spasms to reduce blood loss. Collagen on the vessel wall is exposed and the damaged endothelium releases Von Willebrand factor which binds to collagen. The A1 domain of Von Willebrand factor also forms links between the platelets' glycoprotein Ib/IX/V and the collagen fibrils. This allows activated platelets to adhere and form a platelet plug that temporarily arrests bleeding and this constitutes primary hemostasis.(33)

The coagulation proteins are vital in achieving secondary hemostasis by the function of clotting factors. These clotting factors include: factors I – XIII. The coagulation process is divided into the intrinsic and extrinsic pathways which merge to a common pathway that functions to form a stable fibrin clot (34),The intrinsic pathway commences with activation of factor XII to XIIa. This occurs when collagen is exposed during vascular trauma and is mediated in the presence of kininogen. XIIa then activates factor XI to XIa and consequently, XIa activates factor IX to IXa. Factor IXa together with activated factor VIII (VIIIa) leads to the activation of factor X to Xa in the presence of calcium and phospholipids and this leads to

the common pathway. In the laboratory, intrinsic pathway function is measured as the partial thromboplastin time (35).

The extrinsic pathway starts when tissue injury leads to activation of factor VII to VIIa. Factor VIIa then activates factor X to Xa in the presence of tissue factor and this leads to the common pathway. In the laboratory, prothrombin time is used to measure the extrinsic pathway (34,35). In the common pathway, activated factor X (Xa) converts prothrombin to thrombin in the presence of factor V as a cofactor. Thrombin then converts fibrinogen into fibrin and also converts factor XIII to XIIIa. XIIIa then stabilizes the fibrin into a fibrin mesh (34,35).Certain factors act as Inhibitors of the coagulation system. These include: protein C, protein S and antithrombin III (34). On the other hand, certain factors potentiate the coagulation system and these include: calcium, phospholipids and thrombin.(35)

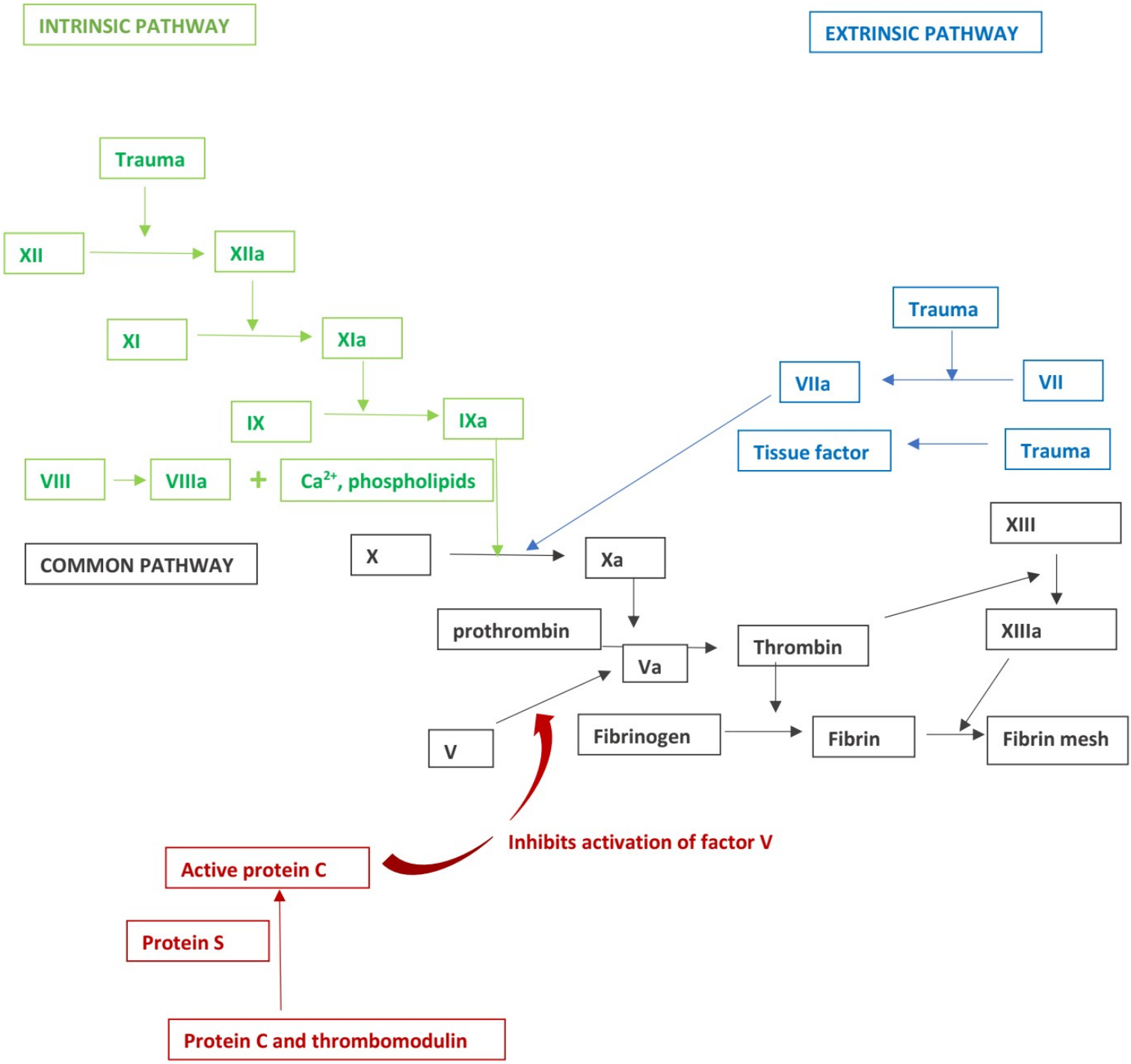


Figure 3: Illustration of the physiology of the Coagulation cascade

1.2.3 Effect of asphyxia on platelets and coagulation proteins

The coagulation system, platelet quantity and quality should function well in order to achieve optimal hemostasis. Hypoxia caused by perinatal asphyxia leads to reduced oxygen delivery to the bone marrow. This results in defect in the bone marrow's ability to produce platelets, reducing the platelet counts in these neonates (36). Christensen et al found that thrombocytopenia occurred in approximately 30% of asphyxiated neonates compared to 5% of matched newborns without perinatal asphyxia (37). A study done by Kumar et al showed that perinatal asphyxia was the third most common risk factor of thrombocytopenia after sepsis and prematurity. It was also noted that thrombocytopenia was associated with increased mortality rates as an independent variable (38).

Hypoxia caused by perinatal asphyxia also leads to reduced oxygen delivery to the liver and this compromises the synthetic function of the liver to produce coagulation factors (39). Hayato et al on a study that looked at the risk factors for disseminated intravascular coagulopathy, found that perinatal asphyxia was strongly associated with disseminated intravascular coagulopathy (40). Srinivasa et al demonstrated similar findings with 55% of the study subjects who were asphyxiated having abnormalities in the coagulation profile. Those with coagulopathy were reported to have poor outcomes (41).

1.2.4 Effect of Therapeutic Hypothermia on platelets and coagulation proteins

The coagulation system which is already dysfunctional in asphyxia is further worsened by TH, which has been shown to reduce the activity of enzymes involved in the coagulation cascade (42). A Cochrane review done in 2013 on TH indicated a statistically significant increased incidence of thrombocytopenia in neonates undergoing TH, with a risk ratio of 1.21 and 95% confidence interval of 1.05 – 1.40. Coagulopathy also occurred more often in the TH group (3). In a study to investigate the safety outcomes of neonates on TH, Eicher et al reported an increased incidence of thrombocytopenia and coagulopathy in neonates on TH which increased the clinical risk of bleeding (43). A systematic review on the major clinical trials done on asphyxiated neonates undergoing TH also reported thrombocytopenia and coagulopathy as some of the complications of the therapy (44). Another review done by Schulzke et al looking at 5 trials on TH reported an increased risk of thrombocytopenia in neonates on TH with a relative risk of 1.47 and 95% confidence intervals of 1.07-2.03 (45).

Boutaybi et al, in a case control study, concluded that asphyxiated neonates on TH had a high predisposition of being thrombocytopenic complicating with intracranial bleeding(46).

Having been reported to have consistent efficacy in reduction of mortality and neurodevelopmental disability in neonates with asphyxia, maximum benefit from TH should be harnessed by ensuring appropriate supportive care is administered to avoid complications from the therapy. Such supportive care includes correction of coagulation abnormalities and severe thrombocytopenia to avert the risk of significant clinical hemorrhage. With hemorrhage being reported in neonates with HIE undergoing TH, transfusion to achieve platelets of >130 x 10^9/L and INR <2 has been recommended to prevent hemorrhage amongst these neonates (47).

1.2.5 Effect of Therapeutic Hypothermia on other systems

Besides the central nervous system, coagulation and hematologic system, therapeutic hypothermia has effect on all other organ systems namely the cardiovascular, pulmonary, gastrointestinal, renal and endocrine system.

1.2.5.1 Effect of TH on the Pulmonary system

Studies have reported cases of acute respiratory distress syndrome (ARDS) in up to 33% of neurologic patients (48). However, the incidence rate of ARDS in patients undergoing therapeutic hypothermia has been reported to be 50% less than those with normothermia (49).This results from a reduction in metabolism and subsequent carbon dioxide production. This finding is demonstrated by reduction in partial pressures of carbon dioxide(PaCO2) and an increased PaO_2-FiO_2 ratio (28).

Due to suppression of inflammatory cytokines by hypothermia, there has always been postulation of increased rates of respiratory infection such as bacterial pneumoniae in patients undergoing the therapy. However, some studies have shown zero to only a small difference in occurrence of infections in patients undergoing therapeutic hypothermia for 24 hours (28).

1.2.5.2 Effects of TH on the Cardiovascular system

A decrease in body temperature to 32 degrees Celsius has an effect of reduced heart rate to roughly 40-45 bpm; which is an expected physiologic response. One adverse effect of therapeutic hypothermia is arrhythmias. Several randomized clinical trials reported

arrhythmias as a side effect of the therapy but there has been lack of consensus about the finding, hence it remains controversial (50,51).

A metanalysis done on seven trials involving 1322 infants to determine whether TH increases the risk of cardiac arrhythmia showed that TH is associated with increased rates of cardiac arrhythmias, hence the need to monitor for arrhythmias during the process of cooling (52).

1.2.5.3 Effects of Therapeutic Hypothermia on liver transaminases

Major clinical trials (Cool Cap trial and TOBY trial) done on babies undergoing Therapeutic Hypothermia showed that it reduced severity of hepatic dysfunction compared to babies who were not being cooled. ALT and AST levels increased during cooling and the levels improved significantly by the end of cooling with the AST levels showing a sharper decline (50,53)

1.2.5.4 Effects of Therapeutic Hypothermia on the Kidney

Up to 72% incidence rate of AKI has been reported in babies with HIE(54,55). Mortality rates of up to 61% have been documented in asphyxiated neonates with AKI (55,56). Randomized controlled trials done indicate that the incidence rates of AKI are lower in babies undergoing Therapeutic Hypothermia in comparison to those undergoing standard treatment.(57)

Table 1: Summary of studies on coagulopathy and thrombocytopenia in asphyxiated neonates undergoing therapeutic hypothermia.

Study title / author/year	**Type of study and study population**	**Findings**
Neonatal thrombocytopenia after perinatal asphyxia treated with hypothermia **Boutaybi et al 2014**	Retrospective case control study 100 neonates	Thrombocytopenia significantly higher in hypothermia group than the control group without increased risk of cerebral bleeding.
Coagulopathy in newborns with hypoxic ischemic encephalopathy treated with therapeutic hypothermia (47) **Katie R Forman et al 2014**	Retrospective study 76 term asphyxiated neonates	Clinically significant bleeding is highly prevalent in asphyxiated babies undergoing therapeutic hypothermia.
Effect of temperature on thromboelastography and implications for clinical use in newborns undergoing therapeutic hypothermia (58) **Katie R Forman et al 2014**	Prospective observational 24 term neonates	17 patients demonstrated a total of 27 bleeding events, including pulmonary hemorrhage, GI bleeding, hematuria.
Cochrane systematic review on cooling for newborns with hypoxic ischaemic encephalopathy (3) **Jacobs et al 2013**	Systematic review 1392 neonates	No significant increase in coagulopathy and thrombocytopenia in whole body cooling. RR 1.14[0.98,1.33]
A systematic review of cooling for neuroprotection in neonates with hypoxic ischemic encephalopathy – are we there yet? (45) **Schulzke et al 2007**	Systematic review 522 neonates	Increased risk of thrombocytopenia in TH group. Relative risk of 1.47, 95% CI: 1.07, 2.03

1.3 Justification and utility

Perinatal asphyxia is one of the leading causes of admissions to the New Born Unit (NBU) in the Low and Middle- Income countries (LMIC). Kenyatta National Hospital (KNH), the main referral hospital in Kenya, has an NBU that admits a large number of neonates with moderate and severe perinatal asphyxia, accounting for almost 20% of the daily admissions. Neonates with moderate and severe perinatal asphyxia are at a higher risk of mortality, adverse neurodevelopmental sequelae, coagulopathy and thrombocytopenia compared to their non-asphyxiated counterparts.

Therapeutic Hypothermia has been established as a neuroprotective intervention in moderate and severe perinatal asphyxia, having shown significant reduction in adverse neurodevelopmental sequalae and mortality in this group of neonates.

The NBU at KNH has now incorporated the use of the MiraCradle™ for providing TH to neonates admitted with moderate and severe asphyxia and meet the criteria for the treatment. Some of the babies who meet the TH criteria, however, are not put on it due to the limited number of the MiraCradle™ sets available. All babies receive the standard supportive care for asphyxia.

Despite having remarkable beneficial effects on the neurological system, TH has been associated with side effects such as increased incidence of thrombocytopenia and coagulopathy. This could predispose the asphyxiated newborns, who already have a compromised coagulation system and reduced platelet counts, to develop clinically significant bleeding.

Occurrence of clinically significant bleeding necessitates early intervention and if this fails, it may result in discontinuation of the TH. This may make a patient not get full benefit of the neuroprotection offered by TH. This adverse outcome can be averted by monitoring of the coagulation function and platelet counts during the period of TH and intervening early.

In KNH, no study has been done to determine the prevalence of coagulopathy and thrombocytopenia in neonates undergoing TH using the MiraCradle™.

This is a novel study that aims to report occurrence of coagulopathy and thrombocytopenia in neonates undergoing TH. Highlighting the occurrence of coagulopathy and thrombocytopenia in these neonates will increase the awareness on the need to monitor these parameters and intervene in a timely manner, in order to improve outcomes of asphyxiated neonates on TH. This will go a long way to ensure that the neonates complete the prescribed TH, hence fully harness the neuroprotective benefits of TH at the KNH-NBU.

So far, most studies on the safety outcomes of therapeutic hypothermia have been done in the developed countries, where TH is also used more, hence data on the African population is limited. This study will add to the pool of knowledge on TH in the African population.

2 Research questions and study objectives

2.1 Research question

- What is the effect of therapeutic hypothermia on coagulation function and platelet counts in neonates with moderate and severe perinatal asphyxia at the Kenyatta National Hospital Newborn Unit?

2.2 Study objectives

Primary objectives

- To determine the effect of therapeutic hypothermia on coagulation profile and platelet counts in neonates with moderate and severe perinatal asphyxia compared to those not on TH.

Secondary objective

- To determine the factors associated with coagulopathy and thrombocytopenia in neonates undergoing TH compared with neonates not on TH.

3 Methodology

3.1 Study Design

The study design was a hospital based prospective cohort study.

3.2 Study Setting

The study setting was at the Newborn Unit of the Kenyatta National Hospital (KNH-NBU), the main national referral hospital in Kenya. The KNH-NBU handles neonates born within KNH and referrals from peripheral facilities, accommodating up to 110 neonates at any given point in time. Some of the conditions managed at the unit include perinatal asphyxia, neonatal sepsis, prematurity, meconium aspiration, neonatal jaundice amongst others.

The unit has a neonatal intensive care unit (NICU) that has a maximum of 7 ventilator beds in use at any given point in time. Other equipment available include 14 CPAP devices, 6 phototherapy machines and 3 MiraCradle™ devices. Perinatal asphyxia accounts for up to 20% of the weekly admissions and approximately 1 - 2 asphyxiated neonates are cooled per week. The unit is run by 7 consultant neonatologists, 9 paediatric residents and 93 nurses trained in neonatal care.

In KNH NBU, TH is done using the MiraCradle™ device to achieve whole body cooling. Temperature is set at between 33-34^{0}C. Vital signs, serum glucose input and out is monitored 4hourly. Feeding is achieved using a nasogastric tube and/or intravenous fluids. Duration of TH is 72 uninterrupted hours and rewarming is then done at 0.5^{0}c per hour for 8 hours to achieve normal body temperatures (36.5^{0}c- 37.5^{0}c). Due to limited number of MiraCradle™ devices, TH is provided to consecutive neonates fulfilling the cooling criteria. This means some neonates who meet treatment criteria for TH miss out on the TH. All neonates admitted having suffered perinatal asphyxia, whether on TH or not, receive supportive care as per the Unit Protocol.

Table 2: Selection criteria for Therapeutic Hypothermia at KNH-NBU

i. Gestational age ≥ 36 weeks, verified using Ballard's Superficial Scores
ii. Age less than 6 hours
iii. Peripartum asphyxia evidenced by an apgar score of 5 or less at 10minutes
iv. Patient requiring resuscitation at 10 minutes of birth
v. Evidence of encephalopathy: Seizures
vi. Moderate or severe hypoxic ischemic encephalopathy as per the Sarnat and Sarnat grading

3.3 Study population

Case Definition of Perinatal Asphyxia

Diagnosis of perinatal asphyxia was based on the definition of "failure to initiate and sustain breathing at birth"(1) plus clinical evidence of Hypoxic Ischaemic Encephalopathy as defined by Sarnat and Sarnat staging (2).The Primary Investigator or trained research assistant examined neonates admitted to the NBU within 12 hours of birth and those who met the criteria for HIE grade 2 and 3 as per the Sarnat and Sarnat grading system were selected for the study.

3.3.1 Cohort 1 (on TH)

Inclusion criteria for cohort 1 (on TH).

- Term neonates
- Evidence of peripartum asphyxia, with at least one of the following:
    - Apgar score of < 5 at 10 minutes
    - Needing resuscitation at 10 minutes
- Evidence of moderate or severe encephalopathy based on Sarnat and Sarnat staging
- Age within 12 hours of birth
- Patient meeting criteria for Therapeutic Hypothermia or already on Therapeutic Hypothermia.
- Informed consent obtained from the caregiver

Exclusion criteria for cohort 1 (on TH).

- Gross congenital anomalies.
- Intrauterine growth restriction.
- Decline to give consent by caregiver

3.3.2 Cohort 2 (not on TH)

Inclusion criteria for cohort 2 (not on TH)

- Term neonates
- Evidence of peripartum asphyxia, with at least one of the following:
    - Apgar score of 5 or less at 10 minutes
    - Needing resuscitation at 10 minutes
- Evidence of moderate or severe encephalopathy based on Sarnat and Sarnat staging
- Less than 12 hours old at the time of recruitment
- Patient meeting criteria for Therapeutic Hypothermia but not on the therapy
- Matched by grade of HIE to a case. Where there was more than one potential control, the one that is of closest age to the case was recruited
- Informed consent obtained from the caregiver

Exclusion criteria for cohort 2 (not on TH)

- Gross congenital anomalies
- Intrauterine growth restriction
- Clinically significant bleeding requiring transfusion with blood products (e.g. bleeding due to birth trauma or coagulopathy)
- The caregiver declines to give consent

3.4 Sampling method

Consecutive sampling of both groups fulfilling the criteria was done until the desired number was achieved.

3.5 Sample size calculation

Sample size was determined using a previous study by Boutaybi et al 2014(46) that gave proportions for the two groups at 59% and 80%. The size was calculated using STATA v 12.2 with the above values and confidence intervals set at 95%.

$$\frac{(Z \propto/2 + Z\beta)2 * (p1(1-p1) + p2(1-p2))}{(p1-p2)2}$$

$\boldsymbol{Z \propto/_2}$ – 1.96 (confidence interval set at 95%)
$\boldsymbol{Z_\beta}$ – 0.2
p1 = 0.59, p2= 0.80 (Boutaybi et al 2014)

The random total sample population was 72 neonates. Because of the small population of asphyxiated neonates being studied at the KNH-NBU, a finite sample correction was done to obtain a convenient sample size

$$n = \frac{n_0}{1 + \frac{(n_0 - 1)}{N}}$$

N = Estimated asphyxia neonates in KNH NBU which is 20% of total neonates admitted to the unit. Total average seen is 300 monthly. 20% of 300 = 60. Duration of data collection 4 months. Total N = 60x4 = 240 and n_0 = 72

$$n = \frac{72}{1 + (\frac{72-1}{240})}$$

= 55 neonates

An attrition rate of 5-10% was factored in bringing the total sample size to 61.

30 study participants were enrolled in therapeutic hypothermia group and 31 in the comparative arm.

3.6 Recruitment procedure

Recruitment of study subjects was done by the Principal Investigator with the help of trained research assistants who were Clinical Officers working in the Paediatric Department.

Training of research assistants included: obtaining informed consent from caregivers, accurate assessment and staging of neonates using the Sarnat and Sarnat staging, accurate filing the data collection tool with details from the patient's or caregiver's file and drawing blood samples for INR, aPTT, platelet counts and urea levels.

Neonates who met inclusion criteria into both arms of the study were identified and recruited into the study after informed consent was obtained from the caregiver. The data collection tool was filled using data extracted from patient's files and baseline blood samples were taken for INR, aPTT, platelet counts and urea levels within the first 12 hours of life.

Blood Sampling Procedure

The Principal Investigator and research assistants ensured sterility by wearing gloves and swabbing the site for blood collection using a spirit swab. A total blood volume of 4.7mls was drawn from the antecubital vein of study participants using a sterile needle for the baseline tests. 2.7mls of blood was collected for coagulation profile in the blue sodium citrate sample bottle. 1ml of blood was collected for platelet count in a purple EDTA microtainer and 1ml of blood was collected for urea in the plain red microtainer. Each sample bottle was allocated a unique study number. Samples for coagulation profile, platelet count and urea were delivered to the laboratory within one hour of collection.

Patients were then followed up and a repeat blood sample was taken for INR, aPTT, platelet and urea within the last 12 hours to completing TH for the TH group and between 60-72 hours of life for the comparative group. A total blood volume of 4.7mls was drawn from the antecubital vein of study participants using a sterile needle for the repeat tests. 2.7mls of blood was collected for coagulation profile in the blue sodium citrate sample bottle. 1ml of blood was collected for platelet count in a purple EDTA microtainer and 1ml of blood was collected for urea in the plain red microtainer. Each sample bottle was allocated a unique study number. Samples for coagulation profile, platelet count and urea were delivered to the laboratory within one hour of collection.

3.7 Laboratory Procedures

3.7.1 Specimen Handling and Analysis

In the Kenyatta National Hospital laboratory, the coagulation profile sample was centrifuged to extract plasma. Assay was run using ACL Elite Pro™ machine which is fully automated. An INR value of > 1.2 and aPTT of >35 sec was used as cut offs for the definition of coagulopathy. These are the standard laboratory cut off values for the Kenyatta National Hospital laboratory. These values are comparable to those used in the Cochrane review on cooling for newborns with hypoxic ischaemic encephalopathy by Jacobs et al (3).

Samples for platelet counts were delivered to the laboratory in the purple EDTA microtainer within one hour of collection and total blood count was done by the automated cell counter – Sysmex XN-1000 haematology analyser. Platelet count was derived from the full hemogram print out. A value of < 150,000 platelets was used to define thrombocytopenia. These are the standard laboratory cut off values for the Kenyatta National Hospital laboratory. These values are comparable to those used in the Cochrane review on cooling for newborns with hypoxic ischaemic encephalopathy by Jacobs et al (3).

Samples for urea were delivered to the Department of Pediatrics laboratory in the plain red 1ml microtainers within one hour of collection and centrifuged for two minutes at 3000 revolutions per minutes to extract serum.

Assay was run using Humastar 600™ which is fully automated.

Urea levels were assayed using photometric method on the Humastar 600™ and the results printed out. A urea value of >8.2mmol/L was used to define uremia. These are the standard laboratory cut off values for the University of Nairobi laboratory. These values are comparable to those used in the Cochrane review on cooling for newborns with hypoxic ischaemic encephalopathy by Jacobs et al (3).

3.7.2 Quality Control

Daily internal quality control and quarterly external quality control is done on the ACL Elite Pro™ machine in the University of Nairobi laboratory to ensure validity of results.

Daily internal quality control and monthly external quality control is done on the automated cell counter - Sysmex XN-1000 haematology analyser in the Department of Paediatrics laboratory to ensure validity of results.

Daily internal quality control and quarterly external quality control is done on the Humastar 600™ machine in the Department of Paediatrics laboratory to ensure validity of results.

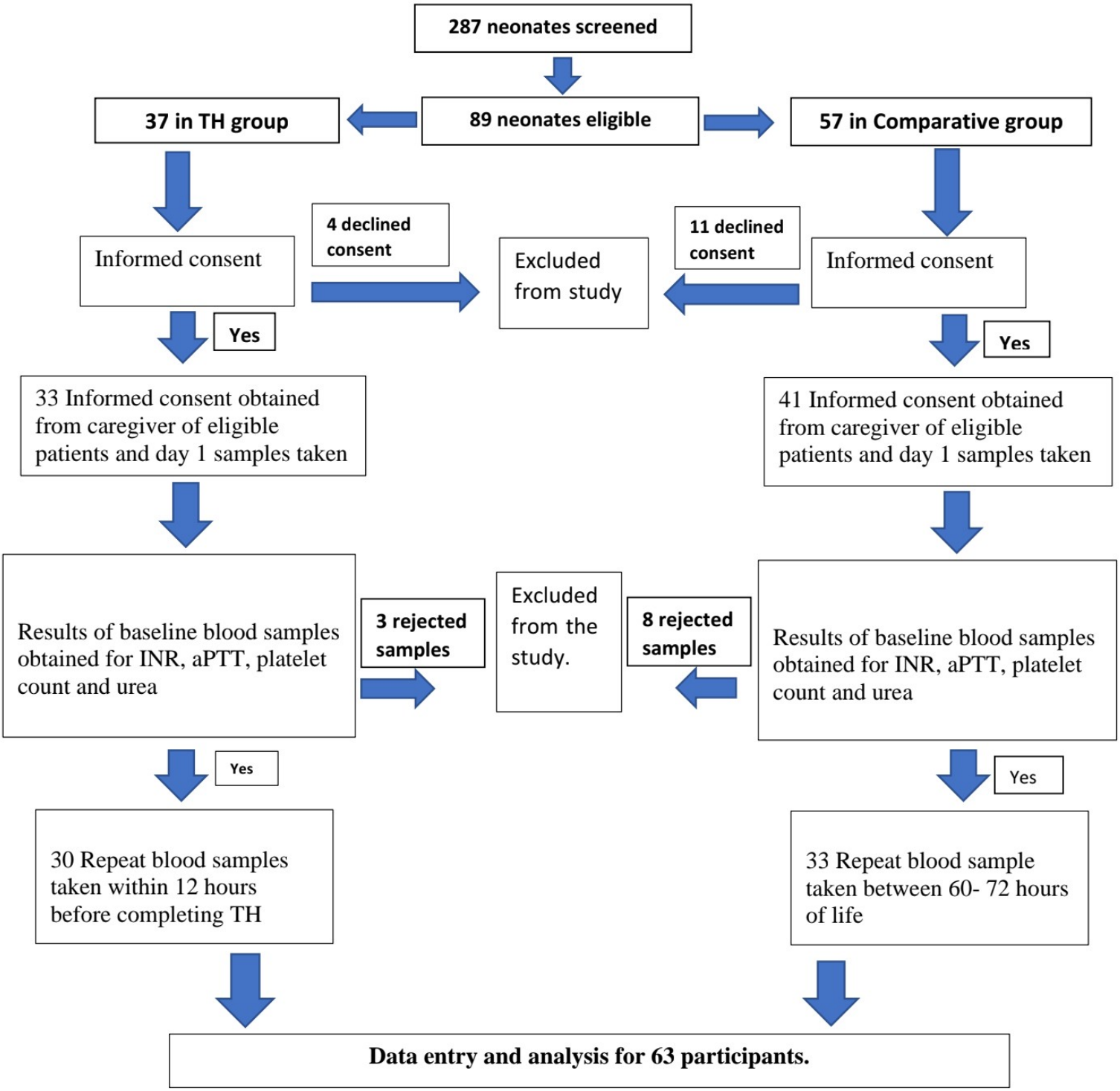


Figure 4: Study procedure flow chart

4 Data management, results and analysis

4.1 Data management

The statistical analysis involved exploratory, descriptive and inferential analysis.

Data analysis was preceded by data cleaning which involved checking for uniformity, outliers and factorization of categorical data in Microsoft Excel. Data was then exported to STATAv12.2 for analysis.

The variables were categorized into nominal, ordinal and continuous variables.

Exploratory analysis involved testing for normality using formal normality tests (Shapiro Wilk test) and graphical methods (histogram). Outliers were identified graphically using box and whisker plots.

Descriptive statistics included measures of central tendency and dispersion i.e., mean (standard deviation) or median (interquartile range) for parametric and non - parametric continuous variables respectively. Categorical data was described using frequencies and percentages.

Inferential statistics was structured in both the 'between group' and 'within group' formats.

Between group analysis involved comparing results from the therapeutic hypothermia group against the non-therapeutic hypothermia group. The tests used were unpaired/ independent. Statistical significance between group differences in normally distributed variables was tested by parametric methods (2 sample unpaired t test with equal variance and 2 sample unpaired t test with unequal variance – Welch test). Statistical significance between group differences in non - normal distributed variables was tested by non - parametric methods (Mann Whitney U test). Statistical significance between group differences in categorical variables was tested using Chi square. Chi square with Yates' continuity correction was used where expected values were less than 5.

Within group analysis involved comparing initial results (day1) and final results (day 3) in the individual groups i.e., the therapeutic hypothermia group and non - therapeutic hypothermia group. Within group analysis was done for the variables of interest (INR, aPTT, platelets and urea). The tests used were paired/ dependent. Within group statistical

significance in normally distributed variables was tested using the paired T test while non-normally distributed variables used the Wilcoxon Signed Rank test (paired/dependent).

For statistically significant results found in between group and within group analysis, the strength and direction of the relationship was examined further. Correlation was investigated using the Spearman correlation test with 0.7 being the cut off of strong positive correlation and -0.7 for strong negative correlation. Predictor analysis was done using simple linear regression to examine possible contributors to the statistically significant variables. Adjusted R squared was used to investigate possible predictors of any significant coagulation laboratory results. Any results of < 0.5 would indicate poor fitting models thus further interpretation was not done. Multiple linear regression would only be attempted after successful simple linear regression.

4.2 Results

The study screened 287 neonates over a period of 5 months for eligibility after which 224 were excluded for not fulfilling the inclusion criteria. During the study period, there were 8 deaths and 4 rejected samples. Data obtained from participants who died before day 3 of life was included in analysis to avoid selection bias. The 4 patients who had rejected day 1 samples were excluded from the study.

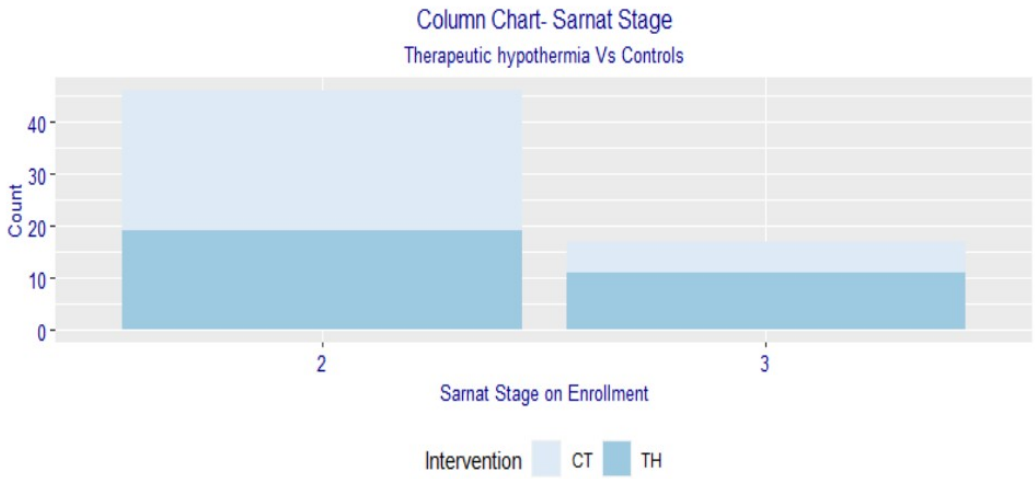
The total study size was 63 with 30 undergoing therapeutic hypothermia and 33 not on therapeutic hypothermia. The results of exploratory data analysis done using the Shapiro Wilk test (95%) revealed 14 non parametric variables and 20 parametric variables. Descriptive statistics was done on the study participants biodata, vital signs, laboratory results and mother's demographic characteristics.

4.2.1 Clinical and sociodemographic characteristics of the study participants

Study participants in both groups were predominantly male (70% in the therapeutic hypothermia group and 65% in the group not on therapeutic hypothermia). The median (IQR) gestational age for both groups was 39(2) weeks. There was no statistically significant difference in the mean (SD) birth weight between the two groups with the mean (SD) birth weight in the therapeutic hypothermia group being 3312 (434) g while that in the group not on therapeutic hypothermia being 3144 (465) g. Both groups had more neonates with moderate asphyxia with the mode of the 5-minute apgar score being 4 in the therapeutic hypothermia group and 6 in the group not on therapeutic hypothermia. There was no

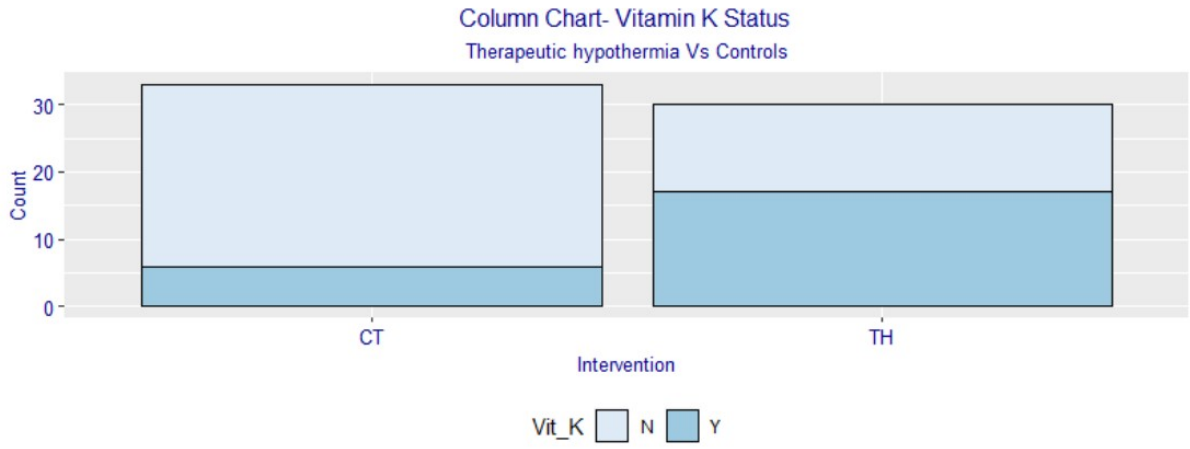
statistically significant difference in sarnat stage between the 2 groups. Figure 5 shows the distribution of Sarnat stage amongst the study participants.

Figure 5: Sarnat stage of study participants



Vitamin K administration was noted to be suboptimal in both groups, with 57% receiving vitamin K at birth in the therapeutic hypothermia group and only 18% receiving vitamin K in the comparative group. A statistically significant difference was noted in the vitamin K administration between the two groups (p = 0.0024). Figure 6 depicts the vitamin K administration status for the study participants.

Figure 6: Vitamin K administration status



The median age at admission in the therapeutic hypothermia group was 2 hours while that in the group not receiving therapeutic hypothermia was 2.25 hours with an IQR of 2.5 in both groups. The median age at initial sample collection was statistically significant between the two groups with therapeutic hypothermia group having a median age of 6.5 hours and

comparative group having a median age of 9.75 hours with an IQR of 3.2 and 5.6 hours respectively. (p = 0.0458)

The median age at final sample collection was 66.6 hours in the therapeutic hypothermia group and 67.5 hours in the group not on TH with an IQR of 8.8 and 8.0 hours respectively. The P values for age at admission and final sample collection were not statistically significant. The participant characteristics are summarized in table 3 below.

Table 3: Neonatal characteristics

Variables	Therapeutic hypothermia group n, (%)	No therapeutic hypothermia group n, (%)	Test	P value	Odds ratio (95% CI)
Sex (Male)	21 (70%)	22 (65%)	Odds ratio	0.7766	1.17(0.40-3.38)
Gestational age**	39 (2)	39 (2)	Mann Whitney U test	0.9100	N/A
Birth weight (grams)*	3312 (434)	3144 (465)	2 sample unpaired T test	0.1545	N/A
Apgar at 5***	4	6	Chi square	0.2031	N/A
Vitamin k status (Yes)	17 (57%)	6 (18%)	Odds ratio	**0.0024**	**5.88 (1.89-18.44)**
Sarnat staging (sarnat 3)	11 (37%)	6 (18%)	Odds ratio	0.1042	2.61 (0.82-8.27)
Age at admission(hrs)**	2 (2.5)	2.25 (2.5)	Mann Whitney U	0.3507	N/A
Age at initial sample collection (hrs)**	6.5 (3.2)	9.75 (5.6)	Mann Whitney U	**0.0458**	**N/A**
Age at final sample collection**	66.6 (8.8)	67.5 (8)	Mann Whitney U	0.4494	N/A

4.2.2 Laboratory investigation results

4.2.2.1 Day 1 laboratory profiles

52 neonates had an INR above 1.2 at day 1 (Therapeutic hypothermia group- 24, No therapeutic hypothermia group- 28) translating to an odds ratio of 0.71 (95% CI 0.19-2.64). The median day 1 INR value for therapeutic hypothermia was 1.37 while that for those not on TH was 1.53 with an IQR of 0.57 and 0.48 respectively. 40 neonates had an aPTT above 35 seconds at day 1 (Therapeutic hypothermia group- 18, No therapeutic hypothermia group- 22) translating to an odds ratio of 0.75 (95% CI 0.27-2.10). The median day 1 aPTT value for therapeutic hypothermia was 36.7seconds while that for those not on TH was 37.5seconds with an IQR of 14.3 seconds and 7.98 seconds respectively.

Seven neonates had thrombocytopenia at day 1 (Therapeutic hypothermia group- 3 No therapeutic hypothermia group- 4) translating to an odds ratio of 0.81 (95% CI 0.16-3.93). The mean day 1 platelet count for therapeutic hypothermia was 252 while that for those not on TH was 229.6 with a standard deviation of 77.5 and 80.8 respectively. The median day 1 urea value for therapeutic hypothermia group was 4.1 while that for those not on TH was 6.0 with an IQR of 1.75 and 4.4 respectively. The day 1 laboratory results are summarized in table 4 and table 5 below.

Table 4: Day 1 laboratory investigation results for coagulation function

Variable	Therapeutic hypothermia	No therapeutic hypothermia	Test	P value
INR**	1.37 (0.57)	1.525 (0.48)	Mann Whitney U	0.1388
aPTT **	36.7 (14.3)	37.5 (7.9)	Mann Whitney U	0.9561
Platelets*	252 (77.5)	229.6 (80.8)	2 sample t test (welch test)	0.2343
Urea**	4.1 (1.75)	6 (4.4)	Mann Whitney U	**0.02862**

*mean (SD) **median (IQR)

Table 5: Odds ratios for Day 1 laboratory investigations for coagulation function

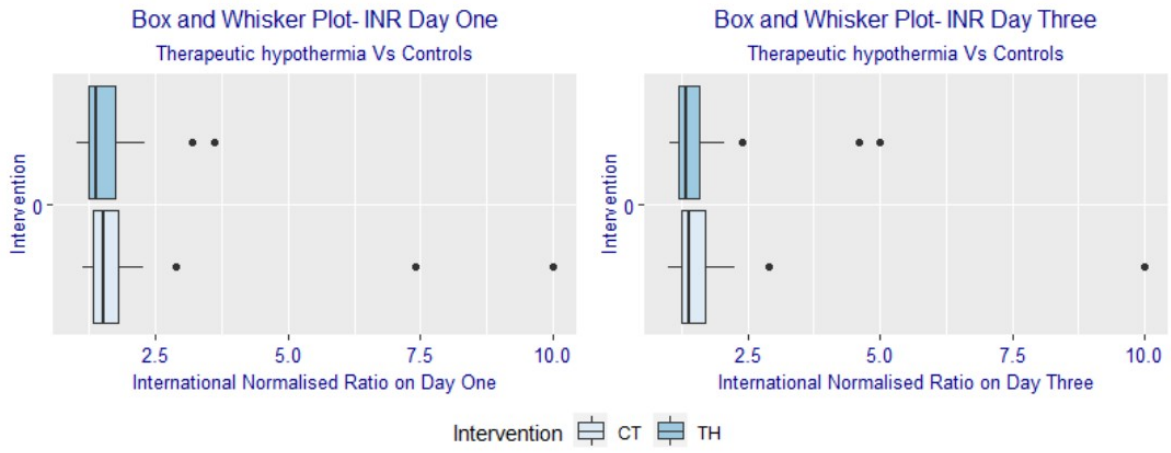
Variable		Therapeutic hypothermia	No therapeutic hypothermia	Odds ratio (95%CI)	P value
INR	>1.2	24	28	0.714 (0.19 -2.64)	0.614
	<1.2	6	5		
aPTT	>35 sec	18	22	0.75 (0.27 – 2.10)	0.584
	<35 sec	12	11		
Platelets	<150	3	4	0.81 (0.16 -3.93)	0.789
	>150	27	29		
Urea*	>8.2	0	9	0.04 (0.017 – 0.106)	**<0.0001**
	<8.2	30	24		

**Haldane correction*

4.2.2.2 Day 3 laboratory profiles

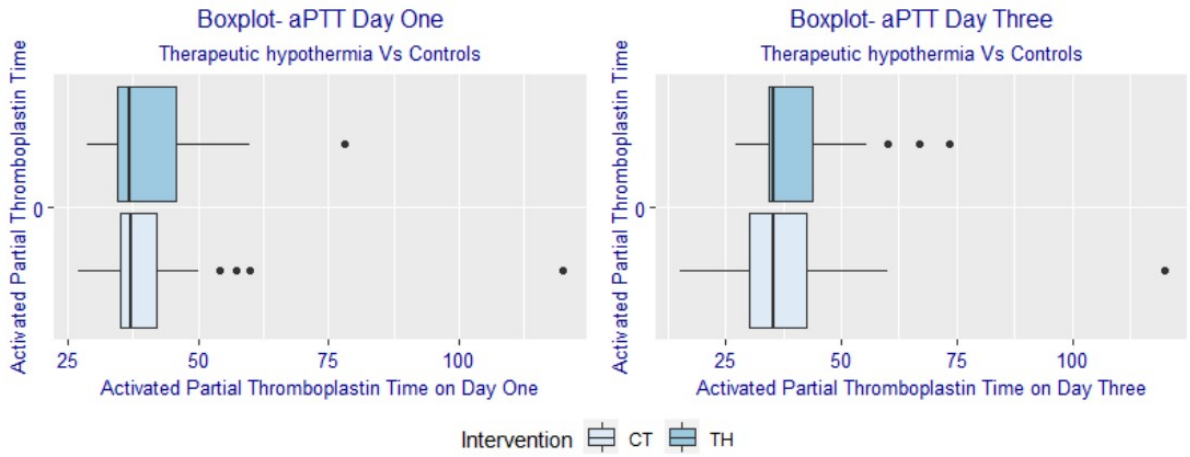
46 neonates had an INR above 1.2 at day 3 (Therapeutic hypothermia group- 20, No therapeutic hypothermia group- 26) translating to an odds ratio of 0.54 (95% CI 0.17-1.66). The median day 3 INR value for therapeutic hypothermia was 1.325 while that for those not on TH was 1.40 with an IQR of 0.38 and 0.45 respectively.

Figure 7: INR day 1 and day 3



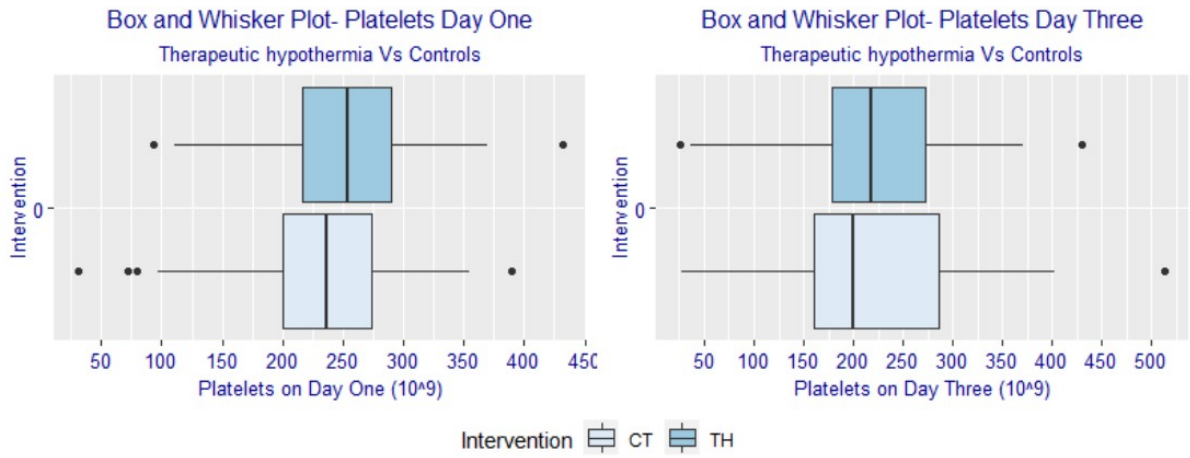
32 neonates had an aPTT of >35 seconds (16 in therapeutic hypothermia group and 16 in the group not on therapeutic hypothermia) translating to an odds ratio of 1.2 (95%CI 0.45 – 3.27).The median day 3 aPTT value for therapeutic hypothermia was 35.35 seconds while that for those not on TH was 35.2seconds with an IQR of 9.7 seconds and 15.5 seconds respectively.

Figure 8: aPTT day 1 and day 3



14 neonates had thrombocytopenia at day 3 (Therapeutic hypothermia group- 6, No therapeutic hypothermia group- 8) translating to an odds ratio of 0.781 (95% CI 0.263 – 2.588) The mean day 3 platelet count value for therapeutic hypothermia was 216.6 while that for those not on TH was 202.7 with a standard deviation of 90.2 and 116.7 respectively.

Figure 9: Platelets day 1 and day 3



The median day 3 urea value for therapeutic hypothermia was 4.0 while that for those not on TH was 5.4 with an IQR of 1.6 and 3.7 respectively. There was a borderline statistically

significant difference in urea values between therapeutic hypothermia group and the comparative group. However, it should be noted that the day 1 (baseline) urea levels in the comparative group was significantly higher than the TH group.

The laboratory results for the participants on day 3 are summarized in table 6 and table 7 below.

Table 6: Day 3 laboratory investigation results for coagulation function

Variable	Therapeutic hypothermia	No therapeutic hypothermia	Test	P value
INR**	1.325 (0.38)	1.4 (0.45)	Mann Whitney U	0.429
aPTT **	35.35 (9.7)	35.2 (15.5)	Mann Whitney U	0.549
Platelets*	216.6 (90.2)	202.7 (116.7)	2 sample t test (welch test)	0.741
Urea**	4 (1.6)	5.4 (3.7)	Mann Whitney U	**0.057**

*mean (SD) **median (IQR)

Table 7: Odds ratios for Day 3 laboratory results

Variable		Therapeutic hypothermia	No therapeutic hypothermia	Odds ratio (95%CI)	P value
INR	>1.2	20	26	0.539 (0.174 – 1.664)	0.282
	<1.2	10	7		
aPTT	>35 sec	16	16	1.214 (0.451-3.269)	0.701
	<35 sec	14	17		
Platelets	<150	6	8	0.781 (0.263 – 2.588)	0.686
	>150	24	25		
Urea	>8.2	1	8	0.108 (0.013-0.922)	**0.042**
	<8.2	29	25		

The mean platelet difference for the therapeutic hypothermia group was – 35.63 while that for the patients not on therapeutic hypothermia was -26.94 with a standard deviation of 63.3 and 94.3 respectively.

4.2.3 Within group analysis

4.2.3.1 Therapeutic Hypothermia Group

In the therapeutic hypothermia group, the means and medians of day 1 and day 3 laboratory results for INR, aPTT, platelets, urea were compared. Of the four parameters, only platelet count was statistically significant with a mean difference of -35.63 x 10^9 p =<0.005.

Table 8: Within group analysis of therapeutic hypothermia

Variable	Day 1	Day 3	Test	P value	95% Confidence Interval***
INR**	1.37	1.325	Wilcoxon Signed Rank Test	0.7701	(0.02) -0.35 to 0.2
aPTT**	36.7	35.35	Wilcoxon Signed Rank Test	0.3064	(0.7) -0.9 to 5.6
Platelets*	252	216.6	Paired T Test	**0.0044**	**(-35.63) -59.3 to -12.1**
Urea**	4.1	4	Wilcoxon Signed Rank Test	0.4362	(0.19) -0.25 to 0.55

**Mean* ***Median*

****Sample estimate- Wilcoxon Signed Rank Test-pseudo median or Paired T Test- the mean of difference*

4.2.3.2 No Therapeutic Hypothermia

In the non - therapeutic hypothermia group, the means and medians of day 1 and day 3 laboratory results for INR, aPTT, platelets, urea were compared. the results of the paired statistical tests of the four variables all had p values larger than 0.05 and hence not statistically significant.

Table 9: Within group analysis of non - therapeutic hypothermia

Variable	Day 1	Day 3	Test	P value	95% Confidence Interval***
INR*	1.53	1.40	Wilcoxon Signed Rank Test	0.0894	(0.17) -0.025 to 0.33
aPTT*	37.5	35.2	Wilcoxon Signed Rank Test	0.2514	(3.15) -3.05 to 8.85
Platelets**	229.6	202.7	Paired T Test	0.1052	(-26.94) -59.84 to 5.96
Urea*	6.0	5.4	Wilcoxon Signed Rank Test	0.5028	(0.29) -0.4 to 0.95

**Median* ***Mean* ****Sample estimate- Wilcoxon Signed Rank Test-pseudo median or Paired T Test- the mean of difference*

4.2.4 Predictor Analysis of Day 1 and Day 3 Platelet change in Therapeutic Hypothermia group

Correlation and Regression

Correlation was done between mean platelet difference and continuous variables. Birth weight, heart rate day1 and day 3, aPTT difference, INR difference and urea difference all had weak positive correlation. Respiratory rate day 1 and day3 had a weak negative correlation.

Simple linear regression was done with adjusted R squared indicating the goodness of fit of the model. All the variables had an adjusted R squared of less than 0.7 invalidating the intercept and slope values which were not interpreted further.

Table 10: Correlation and simple linear regression between platelet difference (day 1 - day 3) and independent variables

Predictor/independent/ X variable (Reference group)	Correlation	Simple linear regression				
	Spearman Correlation	Adjusted R Squared	Intercept	P value	Slope	P value
Sex(Female)	NA	0.03	-34	0.14	-2.23	0.934
Birth Weight	0.17	0.029	-114.5	0.0429	0.03	0.0982
Sarnat Stage (Sarnat 2)	NA	0.034	-37.3	0.0174	4.6	0.8521
Vitamin K Status (No)	NA	0.031	-30.7	0.096	-8.7	0.715
Respiratory Rate(Day 1)	-0.37	0.053	48.5	0.368	-1.4	0.115
Respiratory Rate(Day 3)	-0.22	0.009	33.6	0.595	-1.2	0.268
Heart rate(Day 1)	0.28	0.007	-107.1	0.116	0.6	0.281
Heart rate (Day 3)	0.17	0.054	-113.7	0.0288	0.7	0.1152
INR Difference	0.13	0.103	-33.3	0.0053	-45.9	0.0472
APTT Difference	0.35	0.162	-32.9	0.00436	3.2	0.0157
Urea Difference	0.12	0.069	-28.3	0.337	0.5	0.8724

4.2.5 Moderator analysis for mean difference in platelet count in TH group

Statistically significant differences in the characteristics of the two groups were tested for possible confounding/moderation. (sarnat staging and age at 1st sample collection)

Testing using multiple linear regression with moderator analysis revealed low R squared (< 0.15), with all p values being not statistically significant ($p > 0.05$) showing poor/ no moderator effect.

Table 11: Moderator analysis for age at 1st sample collection and urea levels

	Adjusted R squared
Moderator	**Mean Platelet difference**
Age at 1st sample collection	0.0010
Urea	0.1037

5 Discussion

Safety and efficacy of TH in reducing neurodevelopmental sequelae after asphyxia is well established with large clinical trials and systematic reviews showing that TH is safe with no significant derangements in coagulation function and platelet counts.(3) However, some studies reported side effects of coagulopathy and thrombocytopenia amongst this group of patients.(46) (47) This study highlights that in our set up at Kenyatta National Hospital, New born Unit, therapeutic hypothermia does not cause clinically significant derangements in coagulation function and platelet counts, results which are comparable to systematic reviews done on the same. (3)

We analysed data from 63 neonates, of whom 30 underwent therapeutic hypothermia. Exploratory data analysis via the Shapiro Wilk test segmented the variables into parametric and non-parametric depending on the distribution pattern. This was a necessary step so as to choose the appropriate descriptive and inferential statistics method.

Summary statistics of the admission characteristics of the neonates revealed statistical homogeneity in terms of sex, gestational age, birth weight, Apgar at 5 minutes and Age at admission. This is particularly important since the matching requirements at enrolment used the birth weight and gestational age to prevent selection bias. The results of the t tests and Mann Whitney U revealed successful matching with p values larger than 0.05.

The median age at admission for the therapeutic hypothermia group was 2.0 hours and this correlates with mean age at entry of 1.9 hours in other studies on therapeutic hypothermia (Akisu 2003), which were included in Cochrane systematic reviews.(3)

Vitamin K administration was suboptimal in both groups with the administration status between the two groups being statistically significant. The percentage administration of vitamin K in the therapeutic hypothermia group was 57%, which is more than three times that of those in the comparative group (16%). This was consistent with findings by Coffey et al who noted that prophylactic administration of vitamin K to newborns is relatively well integrated into policy at the global and country levels, but its practice is underutilized.(59) At birth, activities of the vitamin K dependent factors II, VII, IX, and X and the concentrations of the contact factors XI and XII are reduced to about 50% of normal adult values.(34)(35) To investigate this relationship further, simple linear regression was done for vitamin K as the dependent variable against INR difference, aPTT difference and Platelet difference

individually but each revealed poor model fitting with low R values. The study duration may have been too short to illustrate the possible effect of lack of Vitamin K on the coagulation parameters.

The baseline median INR for both groups was noted to be above the cut off of 1.2, with TH group having a baseline median INR of 1.37 (IQR 0.57) and comparative group having a baseline median INR of 1.53 (IQR 0.48). Similar findings were found in a study done by Choudhary et al who noticed elevated INR levels in neonates with perinatal asphyxia. (60) The baseline median aPTT for both groups was noted to be above the cut off of 35, with TH group having a baseline median aPTT of 36.7 (IQR 14.3) and comparative group having a baseline median aPTT of 37.5 (IQR 7.9). These findings are consistent with a study done by Akram et al who reported significantly higher INR and aPTT values amongst neonates with perinatal asphyxia.(61)This indicates that perinatal asphyxia as an independent variable causes derangement in coagulation function. Baseline platelet counts in both groups were within the normal ranges of 150 - 450 x 10^9.

The first primary objective involved comparing measures of coagulation function in neonates undergoing TH and those not on TH. This was based on the null hypothesis that there was no difference between INR and aPTT in the therapeutic hypothermia group and the non-therapeutic hypothermia group. The alternative hypotheses were two sided indicating that there was a difference (either greater or lesser).

There was no statistically significant result for INR and aPTT leading to a failure to reject the null hypothesis. As such based on this data, therapeutic hypothermia as an intervention did not cause a disproportionate change in the INR and aPTT with odds ratio for coagulopathy being 0.539 (0.174 – 1.664). This is consistent with studies that have indicated that birth asphyxia is an independent cause of coagulopathy and TH did not increase the risk of coagulopathy with odds ratio of coagulopathy being 1.07 (0.87 - 1.3) (metanalysis of Shakaran 2002, Eicher 2005, NICHD study 2005, TOBY study 2005, neo.nEURO study 2010 and ICE study 2011.) (3).

The second primary objective involved comparing platelet count in neonates undergoing TH and those not on TH. This was based on the null hypothesis that there was no difference between platelet count in the therapeutic hypothermia group and the non-therapeutic hypothermia group. The alternative hypothesis was two sided indicating that there was a difference (either greater or lesser). Six neonates had thrombocytopenia at day 1 (Therapeutic

hypothermia group- 2, No therapeutic hypothermia group- 4) translating to an odds ratio of 0.88 (95% CI 0.15-5.3). Thirteen neonates had thrombocytopenia at day 3 (Therapeutic hypothermia group- 4, No therapeutic hypothermia group- 9) translating to an odds ratio of 0.74 (95% CI 0.19-2.8). This was consistent with metanalysis of Eicher 2005, NICHD study 2005, TOBY study 2005, neo.nEURO study 2010 and ICE study 2011 that demonstrated a odds ratio of 1.14 (0.98-1.33) (3)

Paired T test of the therapeutic hypothermia group revealed a statistically significant drop in platelet count from day one to day three of -35.63 x10^9 with 95% confidence intervals of -59.3 to -12.1. Correlation testing and simple linear regression done to examine possible contributors to the platelet change revealed low spearman's correlation coefficient and adjusted R squared respectively. However, the drop in platelet count in the therapeutic hypothermia group did not lead to a mean platelet count of less than 150*10^9 and thus was not clinically significant. In the non-therapeutic hypothermia group, there was no statistically significant difference in Day 1 and Day 3 platelet results in the non-therapeutic hypothermia group. No factors were found to be associated with the significant drop in platelet counts in the therapeutic hypothermia group.

5.1 Study strengths and limitations

Strengths of the study included matching of the study participants by age, weight and degree of HIE. This is particularly important since the matching requirements at enrolment limited selection bias.

The second strength of the study was analyzing urea levels in the study participants. Urea as an independent variable can affect platelet counts, causing a confounding effect. This was mitigated by taking a blood sample for urea levels and regression analysis was used to check for correlation between urea levels and the incidence of thrombocytopenia. For all the laboratory parameters, a baseline and repeat sample was taken and these were adequate to demonstrate a change in the laboratory parameters in the two study populations as opposed to a single sample being taken.

Limitations of the study included a small sample size due to limited number of neonates being placed on therapeutic hypothermia. A larger sample size would have had more power if a larger sample size would have been used. The study was also unable to assess the full spectrum of coagulation functions (coagulation factors).

6 Conclusion and recommendations

6.1 Conclusion

In this study, TH has not demonstrated adverse derangements in coagulation function and platelet count. It was however noted that both groups had an elevated INR and aPTT values at baseline, indicating that asphyxia as an independent variable causes derangements in these parameters. TH was not associated with a statistically significant increase in INR and aPTT. A significant drop in the platelets counts in the group undergoing therapeutic hypothermia indicates a need to monitor platelet counts for all patients undergoing therapeutic hypothermia. Vitamin K administration was also noted to be suboptimal in both groups.

6.2 Recommendations

All patients with moderate and severe hypoxic ischemic encephalopathy should have their coagulation function monitored during the period of admission whether they are initiated on TH or not.

Vitamin K should be administered for all neonates admitted as per the essential newborn care protocol.

Conduct further research into long term effects of therapeutic hypothermia.

7 Ethical consideration

Ethical approval was sought from the KNH/UoN research and ethics board. Only patients of consenting parents were enrolled in the study. Non-consenting parents were assured of continued best clinical care and non-discrimination. The investigator did not randomize patients into the respective groups. Patients on therapeutic hypothermia received the treatment on a first come first served basis. Any patient who met criteria for therapeutic hypothermia but missed due to limited number of cooling devices was enrolled into the comparative group. Only blood sample intended for the study was withdrawn and discarded thereafter. No financial implication was transferred to the patients. At all times, confidentiality of patient information was maintained.

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9 Appendices

a. Appendix I: Sarnat and Sarnat Staging

Sarnat and Sarnat staging for severity of Hypoxic Ischaemic Encephalopathy and in extension Perinatal Asphyxia.

A neonate requires to meets 3 or more criteria of any stage to be classified in that stage.

Stage	Stage 1	Stage 2	Stage 3
Level of consciousness	Alert: arouses to wakefulness or Hyper alert	Lethargic /Obtunded: delayed but complete response to external stimuli	Stupor/Coma: not arousable and is non-responsive to external stimuli.
Activity	Normal	Decreased	Absent
Muscle tone	Normal	Mild hypotonia	Flaccid
Seizures	None	Common: focal or multifocal	Uncommon: excluding decerebration
Reflexes			
Moro	Strong, low threshold	Weak, incomplete	Absent
Suck	Weak	Weak or absent	Absent
Autonomic system	Pupils equal and reacting to light; normal heart rate and respirations	Pupils constricted; bradycardia or periodic/irregular breathing	Pupils deviated/ dilated/non-reactive; variable heart rate or apnoea.

b. Appendix II: Data collection tool

Patient Study Identification Number..... Hospital No..... Date.....

Patient/ Neonate details				
Gender	Male [ ]		Female [ ]	
Date of birth (dd/mm/yy)				
Time of birth				
Age in hours				
Gestational age in weeks				
Birth weight (kgs)				
APGAR score				
Mode of delivery	SVD [ ]		CS [ ]	
Vitamin K administered	Yes [ ]		No [ ]	
Vital signs at time of sample collection	Temp	Resp rate	Heart rate	Bp

Modified Sarnat and Sarnat grading system for HIE		
	Stage II HIE	**Stage III HIE**
Level of consciousness	Lethargic	Stupor / coma
Spontaneous activity	Decreased activity	No activity
Posture	Distal flexion, complete extension	Decerebrate
Tone	Hypotonia (focal or general)	Flaccid
Primitive reflexes		
Moro	Incomplete	Absent
Suck	Weak	Absent
Autonomic system		
Pupils	Constricted	Deviated, dilated or non-reactive to light
Heart rate	Bradycardia	Variable
Respiration	Periodic breathing	Apnea
HIE grade =		

Mother's details					
Age					
Parity					
Marital status	Single [ ]	Married [ ]	Separated [ ]	Divorced [ ]	Widowed [ ]
Level of education	None [ ]	Primary [ ]	Secondary [ ]	Tertiary [ ]	
ANC attendance	Yes [ ]		No [ ]		
If yes, Number of ANC clinics attended					
Occupation	Unemployed [ ]	Self employed [ ]	Informal employment [ ]	Formal employment [ ]	
Place of delivery	Home [ ]	Clinic / dispensary [ ]	On transit to hospital [ ]	Hospital [ ]	
Duration of labour	<12hours [ ]		>12hours [ ]		

Laboratory results

Laboratory investigation	Neonate level	Reference ranges
INR		
aPTT		
Platelet count		

c. *Appendix III: Caretaker consent form for cohort 1(Therapeutic hypothermia group - English)*

Patient's study identification number: _____

Date: _____

Study topic: Coagulopathy and thrombocytopenia in neonates undergoing therapeutic hypothermia in Kenyatta National Hospital New Born Unit.

Investigator: Dr. Rachael Kanguha (MBChB)

Paediatric resident, University of Nairobi

Phone number: +254 723-787-178

Supervisors: Prof. Aggrey Wasunna

Department of Paediatrics and Child Health, University of Nairobi.

Dr. Lawrence Owino Okong'o

Department of Paediatrics and Child Health, University of Nairobi.

Principal Investigator's statement:

I am a post graduate student in the paediatric department, University of Nairobi. I am conducting the above titled study and request for you and your baby to take part in the study. The purpose of this consent form is to give you in depth information that will guide you to make an informed decision on whether or not you will take part in the study. Kindly read the consent form carefully. Feel free to seek clarification for any matter that arises concerning the study.

Introduction:

Perinatal asphyxia is a condition where the baby's brain and other organs do not get enough oxygen before during or after birth. Some of the organs affected include the liver, kidney and how the baby's blood clots. Because of this, the function of the baby's organs should be monitored in order to guide doctors on the appropriate management to institute to the baby. Treatment with therapeutic hypothermia (placing the baby in a device that reduces the baby's temperature) has been shown to have long term benefits like reducing the cases of cerebral

palsy and epilepsy. It is however important to monitor how the baby's organs function when the baby undergoes therapeutic hypothermia especially how the baby's blood clots.

The laboratory results obtained from your baby's blood sample will be compared to that taken from babies not undergoing therapeutic hypothermia. The results will help us know how asphyxia has affected how your baby's blood clots and if therapeutic hypothermia further affects the clotting function in your baby.

Study objectives:

The aim of this study is to compare the coagulation function and platelet counts of babies undergoing therapeutic hypothermia and those not on the therapy.

Confidentiality:

The information about you and your baby will be kept in strict confidence and will not be released to any person without your permission. Your baby will be identified by a research number and not name. The laboratory results will be made available to those involved in the medical management of your baby and other babies with perinatal asphyxia.

Benefits:

During the research period you will be advised on the progress of your baby's condition. Information regarding your baby will be given to you and the doctor in charge of treating your baby to improve his/her management. Overall results will be used by healthcare workers to help improve care for babies with perinatal asphyxia. You will not incur any cost by participating in this study.

Risks:

The study will involve taking a blood sample from your baby which may cause a little discomfort. Otherwise the study has minimal risk to the baby.

Voluntarism:

This study is fully voluntary. You are free to withdraw from the study at any one point without any penalty.

Compensation:

There will be no financial reward for participating in this study.

Contact information:

If any questions arise with regards to the study or your participation, feel free to contact the principal investigator, Dr. Rachael Kanguha by calling 0723-787-178.

If you have any questions on your rights as a research participant you can contact the Kenyatta National Hospital-University of Nairobi Ethics and Research Committee (KNH/UON/ERC) by calling telephone No. 2726300 Extension 44102. Email: **uonknh_erc@uonbi.ac.ke.**

Participant consent statement

I, ……as the……..to baby …… have received adequate information, benefits and risks with regards to this study. I agree to participate voluntarily and I can withdraw at any time and my baby will continue receiving the best quality of care. I hereby consent to participate in the study with my baby.

Parent/guardian's signature…….Date:……..

I ……..declare that I have adequately explained to the above participant the study procedure, benefits and risks and answered any arising questions to the best of my ability.

Principal investigator/Research assistant:

Signature:…… Date:……

d. *Appendix IV: Fomu ya kupata idhini la mzazi/mlezi mshiriki kujiandikisha katika utafiti na kupata matibabu ya therapeutic hypothermia (Kiswahili).*

Nambari ya usajili ya utafiti: _____

Tarehe: _____

Utafiti: Kasoro ya jinsi damu inavyo ganda na upungufu wa chembechembe za kugandisha damu katika watoto wachanga walio na asphyxia na kutibiwa kwa therapeutic hypothermia katika wardi ya watoto wachanga kwenye hospitali ya kitaifa ya Kenyatta.

Mpelelezi: **Dr. Rachael Kanguha (MBChB)**

Mwanafunzi, Idara ya paediatrics na afya ya Watoto, chuo kikuu cha Nairobi

Phone number: +254 723-787-178

Wasimamizi: **Prof. Aggrey Wasunna**

Idara ya paediatrics na afya ya Watoto, Chuo Kikuu cha Nairobi.

Dr. Lawrence Owino Okong'o

Idara ya paediatrics na afya ya Watoto, Chuo Kikuu cha Nairobi.

Semi la mpelelezi:

Mimi ni mwanafunzi wa shahada ya pili katika chuo kikuu cha Nairobi. Ninafanya utafiti uliotajwa kwenye ukurasa wa kichwa na ningependa wewe na mtoto wako mhusike kwenye utafiti huu. Kusudi ya fomu hii ya idhini ni kukupea taarifa ya kindani ambayo itakusaidia kuamua kama utashiriki kwenye uchunguzi huu au la. Tafadhali soma fomu hii kwa umakini. Kuwa huru kutafuta ufafanuzi kuhusu jambo lolote linalohusu utafiti huu.

Kianzishi:

Asphyxia ni hali ambayo ubongo wa mtoto pamoja na viungo vya mwili vinakosa oksijeni ya kutosha kabla, wakati na baada ya kuzaliwa. Kati ya viungo ambavyo vinaadhirika ni maini, figo na uwezo wa damu ya mtoto kuganda. Kwa hivyo, jinsi viungo vya mtoto vinavyofanya kazi yastahili kuchunguzwa kwa ajili ya kuelekeza madaktari jinsi ya kumpa mtoto matibabu inayofaa. Matibabu ya therapeutic hypothermia (kuweka mtoto kwenye kifaa

kinachopunguza joto ya mwili) imeonyesha kuwa na manufaa ya muda mrefu kwa mfano kupunguza kesi za ugonjwa wa kupooza kwa ubongo na kifafa. Hata hivyo, ni muhimu kuchunguza jinsi viungo vya mwili vya mtoto vinafanya kazi wakati mtoto anapata matibabu ya therapeutic hypothermia haswa uchunguzi wa jinsi damu inavyoganda.

Majibu ya maabara kuhusu kipimo cha damu ya mtoto wako, yatalinganishwa na ya wale ambao hawapewi matibabu ya therapeutic hypothermia. Majibu haya yatatusaidia kujua jinsi asphyxia imeathiri jinsi damu ya mtoto wako inaganda na kama therapeutic hypothermia iko na athari zaidi.

Malengo ya utafiti:

Kusudi ya utafiti huu ni kulinganisha kasoro ya jinsi damu inavyoganda na upungufu wa chembechembe za kugandisha damu kati watoto wachanga walio na asphyxia wanaopata matibabu ya therapeutic hypothermia dhidi ya wale wasiotumia matibabu hayo.

Usiri:

Taarifa yako nay a mtoto wako yatakuwa siri na hayatapewa mtu mwingine ila kwa idhini yako. Mtoto wako atatambuliwa kwa kutumia nambari ya siri na sio jina lake la kweli. Matokeo ya maabara yatapewa timu inayohusika na matibabu yam toto wako na watoto wengine walio na asphyxia.

Faida:

Kwa muda wa utafiti, utapewa maarifa kuhusu maendeleo yam toto wako. Taarifa kuhusu mtoto wako itapewa wewe na daktari anayesimamia matibabu yam toto wako.Matokeo ya ujumla yatatumika na wafanyikazi wa huduma ya afya kuboresha matibabu ya watoto walio na asphyxia pembeni. Hautapata gharama yoyote kwa kushiriki katika utafiti huu.

Hatari:

Utafiti huu utahusisha kuchukua sampuli ya damu kutoka kwa mtoto na huu unaweza sababisha usumbufu mdogo. Kando ya hayo, utafiti huu utakuwa wa hatari ndogo sana kwa mtoto.

Kujitolea:

Kushiriki kwenye utafiti huu ni kwa hiari kamili ya mshiriki. Uko na uhuru wa kujitoa kwenye utafiti huu wakati wowote bila adhabu yoyote.

Fidia:

Hautapata fidia yoyote ya kifedha kwa kushiriki kwa utafiti huu.

Maelezo ya mawasiliano:

Ikiwa swali lolote litazuka kuhusu utafiti huu ama kuhusika kwako, kuwa huru kuwasiliana na mpelelezi Dr. Rachael Kanguha 0723-787-178.

Ukiwa na swali lolote kuhusu haki yako kama mhusika wa utafiti unaweza kuwasiliana na hospitali ya kitaifa ya Kenyatta – Chuo Kikuu cha Nairobi kamati ya Maadili na Utafiti(KNH/UON/ERC) kwa kupiga simu namba 2726300 Ugani 44102. Barua pepe: **uonknh_erc@uonbi.ac.ke.**

Taarifa ya idhini ya mlezi

Mimi ..... kama ..... kwa mtoto.....nakubali ya kwamba nimepewa maelezo ya kutosha kuhusu utafiti huu, faida, na hatari. Nakubali kushiriki kwenye utafiti huu kwa hiari yang una ninaelewa naweza jiondoa kwa wakati wowote na mtoto wangu ataendelea kupata matibabu ya hali ya juu. Nakubali kushiriki kwenye utafiti huu pamoja na mtoto wangu.

Sahihi ya Mzazi/Mlezi ..... Tarehe .....

Mimi……..nadhibitisha ya kwamba nimeelezea mshiriki wa utafiti huu kikamilifu kuhusu utafiti, faida na hatari na kujibu maswali yaliyozuka kwa uwezo wangu.

Mtafiti mkuu/ Msaidizi wa utafiti .....

Sahihi ..... Tarehe…….

e. *Appendix IV: Consent Form for cohort 2 (Not on therapeutic hypothermia- English)*

Patient's study identification number: _____

Date: _____

Study topic: Coagulopathy and thrombocytopenia in neonates undergoing therapeutic hypothermia in Kenyatta National Hospital New Born Unit.

Investigator: Dr. Rachael Kanguha (MBChB)

Paediatric resident, University of Nairobi

Phone number: +254 723-787-178

Supervisors: Prof. Aggrey Wasunna

Department of Paediatrics and Child Health, University of Nairobi.

Dr. Lawrence Owino Okong'o

Department of Paediatrics and Child Health, University of Nairobi.

Principal Investigator's statement:

I am a post graduate student in the paediatric department, University of Nairobi. I am conducting the above titled study and request for you and your baby to take part in the study. The purpose of this consent form is to give you in depth information that will guide you to make an informed decision on whether or not you will take part in the study. Kindly read the consent form carefully. Feel free to seek clarification for any matter that arises concerning the study.

Introduction:

Perinatal asphyxia is a condition where the baby's brain and other organs do not get enough oxygen before, during or after birth. Some of the organs affected include the liver, kidney and how the baby's blood clots. Because of this, the function of the baby's organs should be monitored in order to guide doctors on the appropriate management to institute to the baby. Treatment with therapeutic hypothermia (placing the baby in a device that reduces the baby's temperature) has been shown to have long term benefits like reducing the cases of cerebral

palsy and epilepsy. It is however important to monitor how the baby's organs function when the baby undergoes therapeutic hypothermia especially how the baby's blood clots.

The laboratory results obtained from your baby's blood sample will be compared to that taken from babies undergoing therapeutic hypothermia. The results will help us know how asphyxia has affected how your baby's blood clots and if therapeutic hypothermia further affects the clotting function in the babies on therapeutic hypothermia.

Study objectives:

The aim of this study is to compare the coagulation function and platelet counts of babies undergoing therapeutic hypothermia and those not on the therapy.

Confidentiality:

The information about you and your baby will be kept in strict confidence and will not be released to any person without your permission. Your baby will be identified by a research number and not name. The laboratory results will be made available to those involved in the medical management of your baby and other babies with perinatal asphyxia.

Benefits:

During the research period you will be advised on the progress of your baby's condition. Information regarding your baby will be given to you and the doctor in charge of treating your baby to improve his/her management. Overall results will be used by healthcare workers to help improve care for babies with perinatal asphyxia. You will not incur any cost by participating in this study.

Risks:

The study will involve taking a blood sample from your baby which may cause a little discomfort. Otherwise the study has minimal risk to the baby.

Voluntarism:

This study is fully voluntary. You are free to withdraw from the study at any one point without any penalty.

Compensation:

There will be no financial reward for participating in this study.

Contact information:

If any questions arise with regards to the study or your participation, feel free to contact the principal investigator, Dr. Rachael Kanguha by calling 0723-787-178.

If you have any questions on your rights as a research participant you can contact the Kenyatta National Hospital-University of Nairobi Ethics and Research Committee (KNH/UON/ERC) by calling telephone No. 2726300 Extension 44102. Email: **uonknh_erc@uonbi.ac.ke.**

Participant consent statement

I, ……as the……..to baby …… have received adequate information, benefits and risks with regards to this study. I agree to participate voluntarily and I can withdraw at any time and my baby will continue receiving the best quality of care. I hereby consent to participate in the study with my baby.

Parent/guardian's signature…….Date:……..

I ……..declare that I have adequately explained to the above participant the study procedure, benefits and risks and answered any arising questions to the best of my ability.

Principal investigator/Research assistant:

Signature:…… Date:……

f. Appendix V: Fomu ya kupata idhini la mzazi/mlezi mshiriki kujiandikisha katika utafiti na kukosa matibabu ya therapeutic hypothermia (kiswahili).

Nambari ya usajili ya utafiti: _____

Tarehe: _____

Utafiti: Matokeo ya biochemikali katika watoto wachanga walio na asphyxia na kutibiwa kwa therapeutic hypothermia katika wardi ya watoto wachanga kwenye hospitali ya kitaifa ya Kenyatta.

Mpelelezi: **Dr. Rachael Kanguha (MBChB)**

Mwanafunzi, Idara ya paediatrics na afya ya Watoto, chuo kikuu cha Nairobi

Phone number: +254 723-787-178

Wasimamizi: **Prof. Aggrey Wasunna**

Idara ya paediatrics na afya ya Watoto, Chuo Kikuu cha Nairobi.

Dr. Lawrence Owino Okong'o

Idara ya paediatrics na afya ya Watoto, Chuo Kikuu cha Nairobi.

Semi la mpelelezi:

Mimi ni mwanafunzi wa shahada ya pili katika chuo kikuu cha Nairobi. Ninafanya utafiti uliotajwa kwenye ukurasa wa kichwa na ningependa wewe na mtoto wako mhusike kwenye utafiti huu. Kusudi ya fomu hii ya idhini ni kukupea taarifa ya kindani ambayo itakusaidia kuamua kama utashiriki kwenye uchunguzi huu au la. Tafadhali soma fomu hii kwa umakini. Kuwa huru kutafuta ufafanuzi kuhusu jambo lolote linalohusu utafiti huu.

Kianzishi:

Asphyxia ni hali ambayo ubongo wa mtoto pamoja na viungo vya mwili vinakosa oksijeni ya kutosha kabla, wakati na baada ya kuzaliwa. Kati ya viungo ambavyo vinaadhirika ni maini, figo na uwezo wa damu ya mtoto kuganda. Kwa hivyo, jinsi viungo vya mtoto vinavyofanya kazi yastahili kuchunguzwa kwa ajili ya kuelekeza madaktari jinsi ya kumpa mtoto matibabu inayofaa. Matibabu ya therapeutic hypothermia (kuweka mtoto kwenye kifaa

kinachopunguza joto ya mwili) imeonyesha kuwa na manufaa ya muda mrefu kwa mfano kupunguza kesi za ugonjwa wa kupooza kwa ubongo na kifafa. Hata hivyo, ni muhimu kuchunguza jinsi viungo vya mwili vya mtoto vinafanya kazi wakati mtoto anapata matibabu therapeutic hypothermia.

Majibu ya maabara kuhusu kipimo cha damu ya mtoto wako, yatalinganishwa na ya wale ambao wanapata matibabu ya therapeutic hypothermia. Majibu haya yatatusaidia kujua jinsi asphyxia imeathiri jinsi damu ya mtoto wako inaganda na kama therapeutic hypothermia iko na athari zaidi kwa watoto wanaopewa matibabu hayo.

Malengo ya utafiti:

Kusudi ya utafiti huu ni kulinganisha kazi ya figo, maini na uwezo wa damu kuganda kati watoto wachanga walio na asphyxia wanaopata matibabu ya therapeutic hypothermia dhidi ya wale wasiotumia matibabu hayo.

Usiri:

Taarifa yako nay a mtoto wako yatakuwa siri na hayatapewa mtu mwingine ila kwa idhini yako. Mtoto wako atatambuliwa kwa kutumia nambari ya siri na sio jina lake la kweli. Matokeo ya maabara yatapewa timu inayohusika na matibabu yam toto wako na watoto wengine walio na asphyxia.

Faida:

Kwa muda wa utafiti, utapewa maarifa kuhusu maendeleo yam toto wako. Taarifa kuhusu mtoto wako itapewa wewe na daktari anayesimamia matibabu yam toto wako.Matokeo ya ujumla yatatumika na wafanyikazi wa huduma ya afya kuboresha matibabu ya watoto walio na asphyxia pembeni. Hautapata gharama yoyote kwa kushiriki katika utafiti huu.

Hatari:

Utafiti huu utahusisha kuchukua sampuli ya damu kutoka kwa mtoto na huu unaweza sababisha usumbufu mdogo. Kando ya hayo, utafiti huu utakuwa wa hatari ndogo sana kwa mtoto.

Kujitolea:

Kushiriki kwenye utafiti huu ni kwa hiari kamili ya mshiriki. Uko na uhuru wa kujitoa kwenye utafiti huu wakati wowote bila adhabu yoyote.

Faidia:

Hautapata fidia yoyote ya kifedha kwa kushiriki kwa utafiti huu.

Maelezo ya mawasiliano:

Ikiwa swali lolote litazuka kuhusu utafiti huu ama kuhusika kwako, kuwa huru kuwasiliana na mpelelezi Dr. Rachael Kanguha 0723-787-178.

Ukiwa na swali lolote kuhusu haki yako kama mhusika wa utafiti unaweza kuwasiliana na hospitali ya kitaifa ya Kenyatta – Chuo Kikuu cha Nairobi kamati ya Maadili na Utafiti(KNH/UON/ERC) kwa kupiga simu namba 2726300 Ugani 44102. Barua pepe: **uonknh_erc@uonbi.ac.ke.**

Taarifa ya idhini ya mlezi

Mimi ..... kama ..... kwa mtoto.....nakubali ya kwamba nimepewa maelezo ya kutosha kuhusu utafiti huu, faida, na hatari. Nakubali kushiriki kwenye utafiti huu kwa hiari yang una ninaelewa naweza jiondoa kwa wakati wowote na mtoto wangu ataendelea kupata matibabu ya hali ya juu. Nakubali kushiriki kwenye utafiti huu pamoja na mtoto wangu.

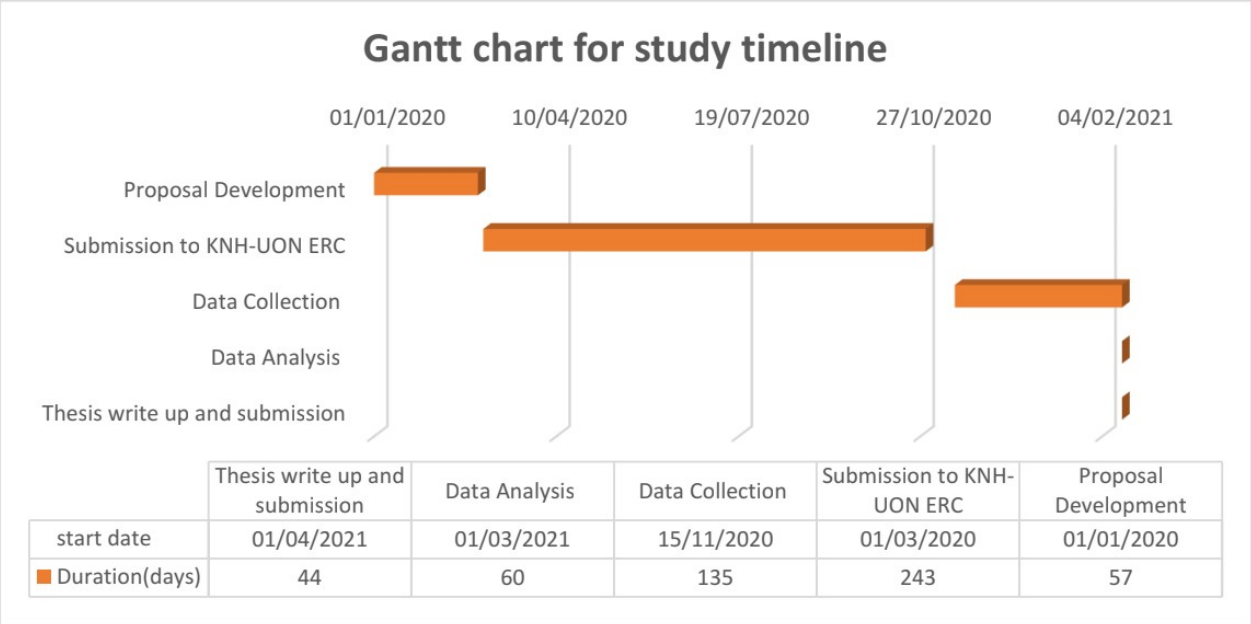
Sahihi ya Mzazi/Mlezi ..... Tarehe .....

Mimi……..nadhibitisha ya kwamba nimeelezea mshiriki wa utafiti huu kikamilifu kuhusu utafiti, faida na hatari na kujibu maswali yaliyozuka kwa uwezo wangu.

Mtafiti mkuu/ Msaidizi wa utafiti .....

Sahihi ..... Tarehe……

g. *Appendix VI: Study timeline*



	Thesis write up and submission	Data Analysis	Data Collection	Submission to KNH-UON ERC	Proposal Development
start date	01/04/2021	01/03/2021	15/11/2020	01/03/2020	01/01/2020
Duration(days)	44	60	135	243	57

h. Appendix VII: Budget

commodity	Price per piece	Number of pieces	Total cost
Notebook	120	2	240
Biros	20	10	200
Pencils	10	10	100
Eraser	30	2	60
File	200	5	1000
Photocopying and printing			10,000
Proposal booklet	2000	5	10,000
Book to ethics committee	2500	1	2500
INR (2 tests per patient)	400x2	70	56,000
aPTT (2 tests per patient)	500x2	70	70,000
Platelet count (2 tests per patient)	500x2	70	70,000
Urea	100x2	70	14,000
Research assistant			30,000
Statistician			30,000
Overall total			294,100