PREVALENCE, ASSOCIATED FACTORS AND MANAGEMENT OF HYPERGLYCEMIA IN NEONATES ADMITTED WITH SEPSIS AT KENYATTA NATIONAL HOSPITAL.

DR. EMELDA A. MANGURO (MBChB, UON)

H58/87616/16

A DISSERTATION SUBMITTED IN PARTIAL FULFILMENT OF THE REQUIREMENTS FOR THE DEGREE OF MASTER OF MEDICINE IN PAEDIATRICS AND CHILD HEALTH OF THE SCHOOL OF MEDICINE, UNIVERSITY OF NAIROBI

2019

DECLARATION

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

Signed.....Date.....

Dr Emelda A. Manguro (MBChB)

Department of Paediatrics and Child Health, University of Nairobi

This dissertation has been presented with our full approval as supervisors:

Signed.....Date.....

Prof. Grace Irimu (PhD, M. Med, MBChB)

Associate Professor and Paediatric Nephrologist

Department of Paediatrics and Child Health, University of Nairobi

Signed..... Date.....

Prof. Rachel Musoke (MBChB, M. Med, Neonatology)

Associate Professor and Neonatologist

Department of Paediatrics and Child Health, University of Nairobi

Signed……. Date…….

Dr Lawrence Owino (MBChB, M. Med, M. Phil)

Lecturer and Paediatric Rheumatologist

Department of Paediatrics and Child Health, University of Nairobi

ACKNOWLEDGEMENTS

I wish to express my appreciation to:

Department of Paediatrics and Child Health University of Nairobi especially my supervisors for their incredible mentorship, dedication, guidance, support and valuable input throughout the study.

All the neonates and their caregivers for their patience and willingness to participate in the study.

My parents, husband Douglas and daughter Sanaya for their overwhelming support without which this would not have been possible.

TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

ABBREVIATIONS

ATP -	Adenosine Triphosphate
GLUT -	Glucose transporter
IMCI -	Integrated Management of Childhood Illnesses
IVH -	Intraventricular haemorrhage
KNH -	Kenyatta National Hospital
NBU -	Newborn unit
NICU -	Neonatal intensive care unit
NIRTURE trial -	Neonatal Insulin Replacement Therapy in Europe trial
PEU -	Paediatric Emergency Unit
SDG -	Sustainable Development Goals
UON -	University of Nairobi
WHO -	World Health Organization
ASPEN -	American Society for Parenteral and Enteral Nutrition
IL -	Interleukin
TNF -	Tumour Necrosis Factor
DIC -	Disseminated intravascular coagulopathy
IV	Intravascular

OPERATIONAL DEFINITION OF TERMS

Neonate - An infant under 28 days of age.

Neonatal hyperglycemia - Plasma blood glucose level of >8.3mmol/l.

Suspected neonatal sepsis - Clinical syndrome characterized by any one or more of the following signs and symptoms of systemic infection: Fast breathing > 60 breaths per minute, convulsions, severe chest wall indrawing, hypothermia $<35.5^0$ C or hyperthermia $\geq 38^0$ C, change in level of activity, inability to feed, grunting and cyanosis with no positive blood culture.

Proven neonatal sepsis - A positive blood culture in suspected neonatal sepsis.

Caregiver- A guardian other than the mother who is directly involved in the care of the neonate who has been recruited into the study.

A high creatinine level - A level of > 130umol/l for neonates aged less than 7 days and > 70 umol/l in neonates more than 7 days of age.

ABSTRACT

Background

Neonatal sepsis is among the leading causes of neonatal mortality globally and locally. Hyperglycemia is one of the metabolic derangements that occur in neonatal sepsis and it is associated with increased morbidity and mortality in neonates. Knowledge on the prevalence, associated factors and current standards of care of hyperglycemia in neonates with sepsis will provide a better understanding of the problem and will help in identifying areas where strategies for prevention and improving care can be applied.

Objectives

The study objectives were to determine the prevalence of hyperglycemia in neonates admitted with suspected or proven neonatal sepsis at Kenyatta National Hospital (KNH), to determine the associated factors and to describe the management of these neonates in terms of fluid management, enteral feeds and use of insulin.

Study Methods

This was a hospital based descriptive cross sectional study carried out among neonates under 28 days of age admitted with suspected or proven sepsis to the KNH newborn unit (NBU) and paediatric wards. Neonates who fit the case definition were recruited after consent was obtained from their mothers or caregivers. Consecutive sampling was applied and participants were enrolled over a randomly selected time block of 8 hours every day. Data of the recruited neonates were collected using a pre tested structured questionnaire. The random blood sugar taken at admission was then recorded and levels above 8.3 mmol/l were considered as hyperglycemia. Neonates noted to have hyperglycemia had additional data on the initial management at admission obtained from their files, treatment sheets and fluid/feeding charts.

Data Management and Analysis

Data were analysed using SPSS version 23. Categorical data were tabulated and summarized as frequencies and proportions while continuous variables were reported as means with standard deviation or medians with interquartile ranges depending on the distribution. The prevalence of hyperglycemia was computed as a proportion along with 95% confidence interval. Univariate associations of factors (independent variables) with hyperglycemia (dependent variable) was explored with chi square test (categorical data) and student's T-test (continuous variables). A p-value of<0.05 was considered significant.

Results

A total of 303 neonates admitted to KNH with a diagnosis of neonatal sepsis were recruited into the study. Hyperglycemia was present in 80 of these neonates yielding a prevalence of 26.4% (95% CI 21.6- 31.8). The Median blood glucose level in the hyperglycemic group was 13.3 mmol/l (IQR 9.8-21.9). Inability to breastfeed[OR 2.17(95%CI 1.05-4.46), p=0.035], hypernatremia[OR 7.08 (95%CI 3.37-14.90), p=<0.001], thrombocytopenia [OR 2.86 (95% CI,1.40-5.88), P= 0.004] and a temperature of <35.5^{0}C [OR 4.96 (0.9-32), (P= 0.46)] were significantly associated with hyperglycemia in the multivariate logistic regression. Data on the initial management of hyperglycemia in neonatal sepsis, at admission, were analysed for 75 out of the 80 neonates found to be hyperglycemic after 5 neonates who had documented contraindications to enteral feeding were excluded for this analysis. For the neonates who were eligible for enteral feeds, 32/75 (42.7%) were not initiated on enteral feeds. Dextrose was prescribed in the intravenous fluids for 39 neonates and 10/39(25.6 %) had more than the recommended amount of dextrose prescribed. 19/75 (25.3%) neonates had insulin prescribed at admission before the other measures of reducing blood glucose levels were applied with 11/19 (57.9%) of these having higher than the recommended starting dose of insulin given and 12/19(63.8%) having intermittent mode of administration prescribed as opposed to the recommended continuous infusion. Appropriate overall management as per the recommendations in terms of all the three components (enteral feeding, amount of dextrose and insulin), was prescribed for 33/75(44%) neonates.

Conclusion

The prevalence of hyperglycemia, at admission, in neonates admitted to KNH with a diagnosis of neonatal sepsis was found to be 26.4%. Inability to breastfeed, hypernatremia, thrombocytopenia and a temperature of <35.5 ^{0}C were significantly associated with hyperglycemia. Appropriate management as per the recommendations (in terms of all the three components combined) was found in 33/75(44%) neonates with the largest gaps in the management being in the initiation of enteral feeds for the eligible neonates and insulin, in terms of dosage and mode of administration.

1.0 INTRODUCTION

Neonatal sepsis accounts for 15% of neonatal deaths worldwide and is the third leading cause of neonatal mortality globally after preterm birth complications (35%) and intrapartum related events(24%)(1). Neonatal mortality in turn accounts for 46% of all under 5 deaths globally(1). In Kenya the main causes of neonatal mortality are birth asphyxia and birth trauma (36.1%), prematurity(24.6%) and sepsis (15.8%)(2).The neonatal mortality rate in Kenya is 22 per 1000 live births and it has shown the slowest rate of decline compared to the other indices of mortality among the under 5 children(3). Efforts aimed at speeding up the rate of decline in mortality among children should therefore be concentrated on the neonatal period with the goal of coming up with more effective preventive and curative measures that target the main causes.

Hyperglycemia is one of the metabolic abnormalities that occur in neonatal sepsis and it is associated with increased mortality and morbidity(4–7). Complications associated with hyperglycemia in neonates include; osmotic diuresis with dehydration and electrolyte imbalance, intraventricular haemorrhage especially in the preterm infants(8), retinopathy of prematurity(9,10) and ventilator dependence which leads to prolonged hospital stay(11).

Neonatal hyperglycemia is defined as whole blood glucose level of >6.9mmol/l (125mg/dl) or plasma glucose level of >8.3mmol/l (150 mg/dl) (12–18). The whole blood glucose levels are lower than plasma levels because of interference by haematocrit. Most clinicians however do not intervene until the blood glucose levels are >10 mmol/l(17,18).

Hyperglycemia is one of the metabolic changes that occur in neonatal sepsis but there is limited data on hyperglycemia in neonatal sepsis. This is because most of the studies on hyperglycemia in neonates focus on preterm and low birthweight infants and are not specific to sepsis while studies on hyperglycemia associated with critical illness or sepsis focus on older children(19). There is currently no international consensus on the optimal management of neonatal hyperglycemia but practice is improving as neonatal units develop local guidelines on the basis of the limited available research(20). This study sought to estimate the prevalence of hyperglycemia in neonates admitted with sepsis, determine the associated factors and to describe the current prevailing management (in terms of fluids, enteral feeds and insulin) as a first step in understanding the problem with an aim of providing information that may be used to improve care.

2.0 LITERATURE REVIEW

2.1 DIAGNOSIS OF NEONATAL SEPSIS

Neonatal sepsis can result in death and significant disability such as cerebral palsy if it is not detected early and managed appropriately. Its diagnosis and definition are challenging because sepsis in neonates presents with nonspecific signs and symptoms which make differentiating it from other medical conditions difficult especially in resource limited settings where access to laboratory tests that support the diagnosis may be limited or not reliable at all times. A highly specific definition of neonatal sepsis is therefore a challenge (or not routinely feasible) in resource limited settings. History and clinical findings can thus be used to make a diagnosis of suspected sepsis and the World Health Organization (WHO) recommends initiation of antibiotics based on the presence of one or more clinical signs of possible severe bacterial infection(21).

The Young infant clinical signs study group did a large multicentre study assessing the independent association of clinical signs and symptoms with neonatal sepsis and came up with an algorithm of 7 signs and symptoms that predict severe illness in children aged 0-59 days which were included in the WHO IMCI guidelines. These signs and symptoms showed a high sensitivity of 85% and specificity of 75% in neonates 0-6 days and 74% sensitivity and 79% specificity in 7-59 days. The seven signs and symptoms include temp $<35^0$C, temp$>37.5^0$C, difficulty feeding, convulsions, reduced level of activity, severe chest wall in drawing and respiratory rate >60 breaths per minute (22). A systematic review done added grunting and cyanosis to the algorithm(23).

2.2 EPIDEMIOLOGY AND FACTORS ASSOCIATED WITH NEONATAL HYPERGLYCEMIA

There is a dearth of research on hyperglycemia in neonatal sepsis and the precise global prevalence is unknown. There is no globally accepted definition of neonatal hyperglycemia but neonatal hyperglycemia has been defined arbitrarily as a whole blood glucose level of >6.9 mmol/l and plasma glucose levels of >8.3 mmol/l based on studies. The European Medicines Agency expert meeting criteria for diagnosis of sepsis includes blood sugar of more than 10mmol/l (24). The lack of consensus in the definition of neonatal hyperglycemia has also led to variation in definition making comparison of studies difficult(25).

Locally Njihia *et al* found the prevalence of hyperglycemia among 52 neonates with sepsis at Kisii level 5 hospital to be 23% with use of herbal medication and elevated immature to total neutrophil (IT) ratio being significantly associated with hyperglycemia (19). A retrospective analysis of 75 years' data on neonatal sepsis with positive blood culture at Yale New Haven Hospital found that

hyperglycemia was present in 32.1% of all cases and it was more prevalent in neonates with late onset neonatal sepsis (5-30 days) at 38.1%(26).

Islam *et al* investigated the glycemic status and effect on neonatal sepsis in a medical college Hospital in Bangladesh. Out of the 62 neonates clinically diagnosed to have neonatal sepsis, 71.2% were normoglycemic, 13.5% hypoglycemic and 15.3% were hyperglycemic. The study also found that mortality was significantly higher among the septic newborns with hyperglycemia ($P<0.05$) (27).

Ahmad *et al* did a study in Pakistan that investigated the blood glucose levels of 502 neonates with suspected and proven sepsis and determined the association of the blood sugar level with mortality. They found that 9.9% of the neonates had blood glucose levels below 40 mg/dl (2.2mmol/l), majority of the neonates (64.1%) had blood sugar levels between 40-100mg/dl(2.2-5.5mmol/l), 18.9% had levels of 101-200 mg/dl (5.6-11.1 mmol/l) and 6.9% had levels >200 mg/dl(>11.1mmol/l). The mortality rate was highest in the group that had blood glucose level of >11.1 mmol/l at 48.6% followed by the group with levels < 2.2 mmol/l at 32% ($p<0.001$)(28).

A prospective cross-sectional study on the frequency of neonatal hyperglycemia, clinical aspects and short term outcomes done by Mohammed *et al* in Khartoum found that the frequency of neonatal hyperglycemia (defined as whole blood glucose of 6.9mmol/l or plasma glucose of 8.3mmol/l) in neonates admitted to the neonatal intensive care unit (NICU) was 24.6% with sepsis occurring in 78.8% of the neonates found to have hyperglycemia. Most of the neonates found to be hyperglycemic were males at 61.2%. Preterm infants accounted for 49.4% of all the hyperglycemic neonates while term babies were 50.6%. Hyperglycemia was more common in neonates less than 7 days of age at 61.2% compared to neonates aged 8 to 14 days where the frequency was 25.9%. Acute kidney injury occurred in 11.9% of the neonates and hypernatremic dehydration in 4.7%. Majority of the mothers (88.2%) had no chronic illness during pregnancy but 7.1% had hypertension and 4.7% had diabetes(29).

Akmal *et al* did a prospective comparative cross-sectional study in low birth weight babies in Egypt where they compared a group of hyperglycemic neonates with a group of euglycemic neonates in terms of neonatal parameters, antenatal factors, postnatal factors, complications and outcomes. The study found that late onset neonatal sepsis was significantly associated with hyperglycemia ($p=0.001$). Other factors associated with hyperglycemia included gestational age ($r=-0.30$, $P=0.019$) placental insufficiency ($p=0.04$), inotropes ($P=0.001$) and milk intake after birth where less milk intake was associated with hyperglycemia ($p=0.007$)(30).A study by Yoon *et al* also showed that

hyperglycemia was less common in the first 24 hours in neonates who had been started on enteral feeds(31).

Prospective cohort analysis of the Neonatal Insulin Replacement Therapy in Europe trial done by Beardsall *et al* showed that prematurity, small for gestational size, lipid infusions and sepsis are independent risk factors for neonatal hyperglycemia(32).

Hyperglycemia has also been significantly associated with dexamethasone, theophylline and catecholamines which are some of the drugs used in neonates(33).

2.2 NORMAL GLUCOSE METABOLISM IN NEONATES

2.2.1 Glucose Homeostasis in the Newborn

Delivery poses a challenge for the newborn since the continuous supply of glucose from the mother through the placenta that occurs in utero is cut off once the umbilical cord is severed and the neonate has to maintain the blood sugar levels within the normal range despite intermittent feeds(34,35). This is overcome by hormonal and metabolic adaptations that maintain a balance between glucose production and utilization by the body tissues. The main hormones involved are insulin and the counter regulatory hormones such as glucagon, cortisol, catecholamines and growth hormone. This transitional state makes the maintenance of euglycemia difficult especially for the ill, premature or low birth weight neonates(36).

In the neonatal period and beyond, blood glucose is obtained from various sources including: i) the feeds through intestinal absorption, ii) glycogenolysis which is the breakdown of glycogen, the storage form of glucose found in the liver, and iii) gluconeogenesis which is the synthesis of glucose from substrates generated from carbohydrate, protein and fat metabolism.

Once in the blood stream, glucose is utilized by tissues and organs that have different characteristics. The brain uses glucose independent of insulin since the large blood to brain glucose concentration gradient in the brain drives the facilitative diffusion mediated by the glucose transporters. The liver, gut and erythrocytes increase glucose utilization with increase in plasma concentration regardless of plasma insulin concentration since the glucose transporters in the membranes of the cells in these tissues are up regulated by increase in blood glucose concentration. Adipose tissue, skeletal muscle and cardiac muscle are however dependent on insulin for their glucose uptake(36).

2.2.2 Glucose Transporters

Glucose uptake into tissues and organs occurs via glucose transporters(GLUT) that are expressed in a tissue specific manner (34,37).There are several GLUT but the most important ones that have clearly defined roles are:

i. GLUT 1 - found in most cells of the body including erythrocytes and is the most predominant in fetal life. It has a high affinity for glucose hence it is able to transport glucose even during hypoglycemia and is responsible for basal uptake(38). In the brain GLUT 1 is responsible for transport of glucose across the blood brain barrier

ii. GLUT 2 - located in the liver, pancreatic β cells, intestinal mucosa and the kidney. Has a low affinity for glucose and forms a glucose sensing apparatus together with glucokinase enzyme in the pancreatic beta cells and hepatocyte.

iii. GLUT 3 - found in the brain and the testis and regulates the uptake of glucose by neuronal cells. It has a high affinity for glucose

iv. GLUT 4 - found in adipose tissue, cardiac muscle and skeletal muscle. It is localized intracellularly and is expressed in response to insulin hence glucose transport into these tissues is insulin-dependent.

In fetal life, GLUT 1 is the most predominant form but after birth its levels decline as other isoforms such as GLUT 2 and GLUT 4 increase. GLUT 4 levels increase with the growth of tissues in which it is expressed in such as skeletal muscle and this contributes to the insulin insensitivity experienced in preterm and low birth weight infants(19,34).

2.2.3 Role of the Various Hormones in Glucose Homeostasis

Insulin is secreted by pancreatic beta cells and its secretion is regulated mainly by blood glucose levels. In the setting of high blood glucose levels, for example after a meal, the glucose is transported into the pancreatic beta cells by the GLUT 2 transporter and is phosphorylated by glukokinase before being metabolized further to produce ATP. The increase in ATP levels then leads to the closure of ATP dependent K+ channels causing depolarization and calcium influx that in turn leads to the release of insulin from the secretory granules in the beta cells by exocytosis. Insulin has several roles in glucose metabolism that result in net reduction of blood glucose levels. It reduces hepatic production and increases hepatic and peripheral glucose utilization through the following mechanisms(34,35,39,40);

i. Inhibition of glycogenolysis and gluconeogenesis by inhibiting glucagon production. It also inhibits proteolysis and lipolysis hence reduces substrates for gluconeogenesis.

ii. Increases uptake of glucose into adipose tissue and muscle by increasing expression of GLUT 4.
iii. Increases glycolysis in adipose tissue and muscle.
iv. Stimulation of glycogen synthesis in the liver.
v. Promotes lipogenesis and protein synthesis.

In the setting of low blood glucose levels, for example in the fasting state, counter regulatory hormones are stimulated in addition to the decreased insulin secretion because of decreased ATP.

Glucagon is a hormone produced by the pancreatic α cells in response to hypoglycaemia and it counteracts the action of insulin by promoting glycogenolysis and gluconeogenesis in the liver through its receptors(34,35,41) leading to a net effect of increased blood glucose level.

Catecholamines increase glycogenolysis and gluconeogenesis in addition to supressing insulin secretion. Growth hormone and cortisol stimulate lipolysis hence increasing circulating free fatty acids that are substrates for gluconeogenesis, they also reduce insulin mediated glucose uptake(35,42).

2.3 PATHOPHYSIOLOGY OF HYPERGLYCEMIA IN NEONATAL SEPSIS

Critical illness is associated with stress and the body mounts a response to maintain normal homeostasis during the illness. Neuroendocrine response to stress and inflammation is characterized by activation of the hypothalamic pituitary adrenal axis and the sympathetic nervous system leading to increased production of the counter regulatory hormones cortisol, epinephrine, norepinephrine and growth hormone (38,43,44). These hormones plus glucagon and the pro inflammatory cytokines produced in sepsis cause hyperglycemia through increased gluconeogenesis, increased glycogenolysis, relative insulin deficiency and decreased glucose uptake. A summary of the role of the Various Mediators of Stress Induced Hyperglycemia is given in table 1.

Table 1: Role of the Various Mediators of Stress Induced Hyperglycemia(16,38)

Mediator	**Mechanism**
Glucagon	Increased hepatic glycogenolysis and gluconeogenesis
Catecholamines	Increased gluconeogenesis and glycogenolysis Decreased uptake of glucose by muscle and adipose tissue by inhibiting insulin binding and translocation of GLUT 4 Epinephrine directly supresses insulin production Norepinephrine increases lipolysis hence promotes gluconeogenesis
Glucocorticoids	Decreased uptake of glucose by adipose tissue and muscle by inhibiting translocation of GLUT 4 Increased lipolysis hence gluconeogenesis
Growth hormone	Peripheral resistance to insulin by reducing insulin receptors and impairing their activation Increased lipolysis hence increases substrates for gluconeogenesis
Pro inflammatory cytokines (TNFα, IL1 and IL6)	Skeletal muscle and adipose tissue insulin resistance Hepatic insulin resistance Suppress insulin release and activate pancreatic α cells leading to increased glucagon secretion

In addition to the above mechanisms, solutions such as dextrose and lipids used for nutritional support can contribute to hyperglycemia. The ability to suppress endogenous glucose production in the presence of exogenous glucose is reduced in sepsis because of the hepatic resistance to insulin, relative insulin deficiency and the gluconeogenesis effect of the counter regulatory hormones. Uptake of glucose is also decreased because of peripheral resistance to insulin(45). Lipid emulsions that form part of the parenteral nutrition also provide free fatty acids that are oxidized in preference to glucose. Lipids also supress the hepatic and peripheral actions of insulin which enhances gluconeogenesis especially in the very low birth weight babies(18).

Drugs such as dexamethasone used in the prevention of chronic lung disease(46), catecholamines used for inotropic support and methylxanthines have also been implicated in the pathophysiology of hyperglycemia(30).

2.4 CLINICAL PRESENTATION AND COMPLICATIONS OF NEONATAL HYPERGLYCEMIA

Hyperglycemia can result in significant glycosuria and osmotic diuresis leading to dehydration and electrolyte derangement. It also increases plasma osmolality in that a rise in glucose concentration by 1 mmol/l(18mg/dl) leads to increase in osmolality by 1 milliosmole. The increase in plasma osmolality in turn leads to brain cell dehydration, capillary dilatation and intraventricular haemorrhage(IVH) especially in the preterm neonates who have fragile blood vessels(4,8). The electrolyte imbalance and IVH may present clinically as convulsions, bulging fontanelle and altered level of consciousness resulting into clinical syndromes that mimic neonatal meningitis(47) or neonatal sepsis. Dehydration in neonates has been associated with weight loss and hypovolemia which leads to reduced organ perfusion which can result in acute kidney injury and metabolic acidosis.(48)

Hyperglycemia has been shown to affect white blood cells function since it reduces their responsiveness to inflammatory mediators. It also inhibits opsonisation by causing glycation of the complement system factors, increases the concentration of inflammatory mediators and increases generation of reactive oxygen species by the leucocytes(38). The net effect of all the above is worsening of the inflammation and increased severity of the infection. Another complication associated with hyperglycemia is retinopathy of prematurity(10,49).

Hyperglycemic has been shown to correlate with prolonged ventilator dependence and increased length of hospital stay in septic infants(50).

Hyperglycemia is therefore a ‘multiorgan dysfunction’ condition and it is not surprising that mortality has also been shown to be higher among ill neonates with hyperglycemia(11).

2.5 MANAGEMENT OF NEONATAL HYPERGLYCEMIA

There are controversies surrounding the management of hyperglycemia in neonates. An online survey done in 27 tertiary neonatal units by Alsweiler *et al* in Australasia showed a wide variation in the definition and management of neonatal hyperglycemia among the neonatal units(51). A systematic review of trials on interventions for treatment of hyperglycemia in very low birth weight neonates by Bottino *et al* found two eligible trials and concluded that evidence from the trials was insufficient to determine the effects of treatment of hyperglycemia in very low birth weight

neonates on death or major morbidities. The review recommended larger randomized trials to determine whether and how hyperglycemia should be treated(52).

Some of the approaches recommended for the management of neonatal hyperglycemia include:

i. Normalizing physiology by diagnosing and treating any underlying illness such as sepsis(12,15,18,53,54)

ii. Elimination of medications predisposing to hyperglycemia such as dexamethasone and catecholamines(12,18)

iii. Limited glucose infusion rates to what is required to maintain normal blood glucose.

The rate of glucose production by the neonate's liver during fasting, which is defined as 3 to 4 hours after birth without feeding or 8 to 9 hours after the last feed, is estimated to be 4 to 6 mg/kg/min. This is higher than the adult rate of 2 mg/kg/min because of the higher metabolic rate and brain body weight ratio(34). The preterm may require additional 2-3 mg/kg/min and sick neonates require even slightly more. The maximal oxidative capacity in the neonate is 12mg/kg/day so the rate of infusion should not exceed that(17). 10% dextrose administered at 100mls/kg/day is estimated to provide approximately 7mg/kg/min of glucose. The rate and/or concentration can be reduced in the setting of hyperglycemia. Glucose restriction can however result in catabolism and growth restriction so if hyperglycemia persists and enteral feeds are contraindicated, insulin therapy should be initiated alongside the dextrose infusion.

iv. Early enteral feeds

Enteroendocrine cells produce the incretin hormones glucagon like peptide 1 and glucose dependent insulinotropic peptide in response to enteral feeds(18,55,56). These hormones stimulate production of insulin by the pancreatic beta cells and hence better control of blood glucose levels in neonates who are fed enterally(17,57) A study by Salis et al showed that glucagon like peptide was significantly higher in enterally fed neonates compared to non-fed neonates regardless of post menstrual age ($p=0.0009$) leading to better glycemic control(57).

v. Reservation of insulin for persistent or severe hyperglycemia

- A Cochrane review of trials on insulin for the treatment of hyperglycemia in very low birth weight infants found that insulin allowed optimal glucose infusion rates leading to increased total glucose intake and energy intake associated with better weight gain but it had no effect on complications associated with hyperglycemia(52).The evidence was however insufficient and the review recommended larger trials. These findings were

supported by the Neonatal Insulin Replacement Therapy in Europe (NIRTURE) trial that also showed no impact on primary and secondary outcomes but an increase in mortality at 28 days in the early insulin therapy group(58)

- Hypoglycemia has been reported as one of the complications associated with intensive insulin therapy in neonates(52,58,59) and it was one of the reasons for the termination of the NIRTURE trial. A study by Sacha c *et al* in Netherlands where they assessed the efficacy and safety of tight glucose control in critically ill term neonates noted that hypoglycemia occurred more frequently in neonates compared to older children. They recommended additional safety approaches when using insulin as further studies on use of insulin in this population are carried out(60)
- Insulin has been recommended for persistent hyperglycemia after all the other measures above have failed(12,53,54,61,62)

Table 2: Summary of the recommendations for the management of neonatal hyperglycemia

Source	Recommendations
Rennie and Robertson's textbook of neonatology(54)	<u>Steps in the management of neonatal hyperglycemia</u> • Seek and treat underlying causes such as sepsis • Careful management of intravenous fluid prescriptions so that glucose infusion rates are kept between 4-6mg/kg/min • Insulin for severe hyperglycemia associated with glycosuria not responding to the first 2 steps of management • Introduction of enteral feeds as soon as it can be tolerated
Avery's diseases of the newborn(53)	• Treatment of the underlying causes such as sepsis • Close glucose monitoring (1-2 hrs) plus decreasing rate of glucose administration to 3 mg/kg/min • Insulin treatment if necessary, after above, to be started at a low dose
A.S.P.E.N clinical guidelines(12):	In persistent hyperglycemia in the neonate receiving parenteral nutrition insulin may be used only after other methods of glucose control such as reduction of glucose infusion rates, elimination of medications predisposing to hyperglycemia and correction of underlying causes such as sepsis have failed
Care of the newborn: A handbook of	• Decrease the amount of glucose administered by lowering rate or concentration

primary care(46)	• Insulin may be required if glucose concentrations exceed 200mg/dl (11.1mmol/l) despite minimal glucose infusion rates • Continuous insulin infusion as necessary (to be started at 0.05 units/kg/hour with a maximum rate of 0.1 units/kg/hr) • Frequent blood glucose monitoring • Early amino acid administration to premature neonates since it improves glucose tolerance
Neonatal Medicine Formulary consensus group 2017: Insulin for hyperglycemia(63)	• Insulin is indicated for treatment of persistent hyperglycemia • Starting dose of 0.05 units/kg/hr with a dose range of 0.01 units/kg/hr to 0.1units/kg/hr to be titrated depending on blood glucose concentration with a target of 8 to 10mmol/l • Monitoring of glucose

3.0 STUDY JUSTIFICATION AND UTILITY

Neonatal hyperglycemia is associated with increased morbidity and mortality and it is one of the metabolic changes that occur in neonatal sepsis. There is no data on the prevalence of hyperglycemia in neonatal sepsis at KNH, despite it being the largest national referral and tertiary care hospital in Kenya, and no locally adapted policies or clinical practice guidelines for its management have been implemented.

This study aimed to find out the prevalence of hyperglycemia in neonatal sepsis, factors associated with it and to assess the clinical care given as a first step in understanding the problem. The baseline information provided by the study will determine the burden of the problem and help in identifying areas where strategies for prevention and improving the quality of care of neonates with hyperglycemia can be applied. Improved care will lead to better outcomes as we strive to reduce the neonatal mortality rate to below 12 per 1000 live births by 2030 as per the Sustainable Development Goal 3 targets.

4.0 RESEARCH QUESTION

What is the prevalence, associated factors and management of hyperglycemia in neonatal sepsis at Kenyatta National Hospital (KNH) paediatric wards, newborn unit (NBU) and paediatric emergency unit (PEU)?

4.1 STUDY OBJECTIVES

4.1.1 Primary objective

To determine the prevalence of hyperglycemia at admission in neonates 0 to 28 days admitted to KNH paediatric wards and the NBU with a diagnosis of suspected or proven neonatal sepsis.

4.1.2 Secondary objectives

a. To determine the factors associated with hyperglycemia in neonates diagnosed with proven or suspected sepsis.
b. To assess the initial management, at admission, of hyperglycemia in neonates admitted with proven or suspected sepsis in terms of fluid management, enteral feeds and insulin therapy.

5.0 STUDY METHODOLOGY

5.1 STUDY DESIGN

The study was a hospital based descriptive cross sectional study.

5.2 STUDY SITE

The study was carried out at KNH Paediatric wards, NBU (newborn unit) and PEU (Paediatric Emergency Unit). Kenyatta National Hospital is the largest national tertiary teaching and referral hospital in Kenya. The NBU admits an average of 150 -180 neonates a month with approximately 20% of the neonates being admitted with a diagnosis of sepsis while the paediatric wards admit an average of 60-80 neonates a month with approximately 90% of them being admitted with a diagnosis of sepsis (source: KNH Medical Records Department). Several factors determine whether a neonate is admitted to the NBU or paediatric wards. The admission criteria for NBU include:

- All neonates less than 24 hours of age who require admission including those delivered at home or referred from other facilities.
- All neonates weighing less than 1.8 kilograms requiring admission regardless of age and place of delivery.
- Critically ill neonates requiring mechanical ventilation. They are admitted to the neonatal intensive care unit which is located within the newborn unit regardless of age and weight.
- Neonates delivered at KNH who are not yet discharged home from the postnatal wards and require in-patient management.

Neonates who do not meet the above criteria are triaged at the PEU and admitted to the paediatric wards. Neonatal admissions and initial management in both the PEU and NBU are done by a paediatric resident (trainee paediatrician). Random blood sugar is routinely taken at admission by the nursing staff at PEU or NBU for all the sick neonates who require hospital admission. Other routine investigations done at admission include a complete blood count and renal function tests. C reactive protein, blood and cerebral spinal fluid culture are taken based on the assessment of the paediatric resident and available resources at the time, for example the culture bottles may not be available all the time.

At the time of the study there were no local guidelines for the management of hyperglycemia. Dissemination of the Kenya Neonatal Guidelines for Hospitals, that contains a section on management of neonatal hyperglycemia, began after the study period had elapsed.

5.3 STUDY POPULATION

The study population included neonates under 28 days of age with an admission diagnosis of suspected or proven neonatal sepsis.

5.4 CASE DEFINITIONS

Suspected neonatal sepsis: Any one or more of the following signs and symptoms; Fast breathing > 60 breaths per minute, severe chest wall in drawing, hypothermia $<35.5^0$ C or hyperthermia $\geq 38^0$ C, change in level of activity, convulsions, poor feeding, grunting, cyanosis(21,24)

Proven neonatal sepsis: Signs and symptoms of sepsis plus a positive blood culture.

Neonatal hyperglycemia: plasma blood glucose level of > 8.3 mmol/L(12,18).

5.5 INCLUSION CRITERIA

Informed parental consent.

Admission diagnosis of neonatal sepsis with or without a positive blood culture.

5.6 EXCLUSION CRITERIA

Admission diagnosis of neonatal sepsis on the day of birth.

Congenital anomalies such as gastrointestinal atresia, gastroschisis, inborn errors of metabolism that contraindicate feeding or may require precautions in feeding.

Major congenital anomalies such as cyanotic heart diseases

5.7 STUDY TOOLS

A structured questionnaire was used to collect data from enrolled participants. Data were extracted from clinical and nursing notes in the patients' medical records, treatment sheets and feeding charts. All entries made on the day of admission were reviewed.

5.8 STUDY PERIOD

The study was carried out from November 2018 to February 2019.

5.9 STUDY OUTCOMES

The study aimed to achieve the following outcomes:

- Determine the proportion of neonates with hyperglycemia out of all the neonates with an admission diagnosis of neonatal sepsis.
- Determine the risk factors of hyperglycemia in neonatal sepsis, by comparing the characteristics of neonates with neonatal sepsis without hyperglycaemia and those with neonatal sepsis with hyperglycaemia.
- Describe the management of hyperglycemia at admission in terms of fluid therapy, enteral feeds and insulin therapy.

5.10 STUDY VARIABLES

Independent variables

This were the factors tested for association with hyperglycemia in neonatal sepsis and they included neonatal characteristics such as age in days, sex, gestational age, mode of delivery, place of delivery and whether they were referred from another facility or not. The other independent variables included the maternal characteristics, such as age, marital status, level of education and employment status, as well as the clinical characteristics of the neonates including the laboratory findings.

Dependent variable

The dependent variable was the presence of hyperglycemia which was defined as a plasma glucose level of >8.3mmol/l.

5.11 SAMPLE SIZE CALCULATION

Sample size was calculated using Fisher's formula(64);

$$n = \frac{Z^2 x\ P(1-P)}{d^2}$$

Where,

n = Desired sample size

Z = value from standard normal distribution corresponding to desired confidence level (Z=1.96 for 95% CI)

P = expected true proportion (estimated at 23.0%, from a study conducted by Njihia GW. et al at the Kisii Level 5 Hospital, found the prevalence of hyperglycemia in neonates admitted with sepsis to be 23.0%.) (19)

d = desired precision (0.05)

$$n_0 = \frac{1.96^2 x\ 0.23(1-0.23)}{0.05^2} = 273$$

A Sample size of 273 was required for the study.

5.12 SAMPLING METHOD

Consecutive sampling method was applied. Participants were enrolled over a period of 8 hours every day, both at the PEU and the NBU. Time was chosen by dividing 24 hours into three 8 hour blocks. A Microsoft Excel 2017 spreadsheet was created with block numbers as column headings while the rows contained the days of the study. Thereafter, randomization and selection of a block was done with the use the RAND function that generated random numbers between 0 and 2 for each day of the study. The block that had the highest assigned random number for each of the study dates was selected. This minimized selection bias.

5.13 STUDY PROCEDURE

Data collection during the study period was done by the principal investigator and two research assistants (RA) with a background of medical training. The RAs were clinical officers. These are health care workers who have undergone a three-year diploma training in clinical medicine and surgery. They assist the medical doctors in managing basic medical conditions. The research assistants were trained for two days on how to screen for the neonates who meet the inclusion criteria, take a focussed detailed history and conduct proper examination in order to obtain all the information required. They were also trained on how to extract information from the patients' records and on how to fill a pretested structured questionnaire that was used for data collection. The structured questionnaire was pre-tested on a sample population, during the RAs training, to determine its validity and reliability in data collection.

Either the principal investigator or one of the research assistants was available at the PEU or the NBU to recruit patients. Neonates already diagnosed with neonatal sepsis in the NBU or PEU were identified at admission and a screening tool (refer to appendix III) adapted from WHO IMCI guidelines and the Kenya Paediatric Protocol 2016(47) was used to determine those who fit the case definition based on the signs and symptoms of suspected sepsis. All the subjects who met the inclusion criteria were included in the study after an informed written consent was obtained from the mother or care giver. This was done in either English or Kiswahili based on the mother/caregiver's preference. The predesigned consent form contained an explanation on the purpose of the study and the study procedures to be carried out (refer to appendices I and II). The principal investigators or research assistants carried out the consent discussion and ensured that the mother/caregiver understood the information in the consent form. They also addressed any questions from the mother/caregiver at this point. Consent was given voluntarily without any coercion and a copy of the signed consent form was given to those who agreed to participate in the study.

The patient s' data were then collected using a two-part pre- tested structured questionnaire (refer to appendix IV). Part 1 contained the demographic variables of the neonate, maternal data including the antenatal history and socioeconomic variables which were obtained by interviewing the mother or care giver. Part II of the questionnaire contained data on the presenting complaints, examination findings, investigations done and management. Data on the presenting complaints were collected by

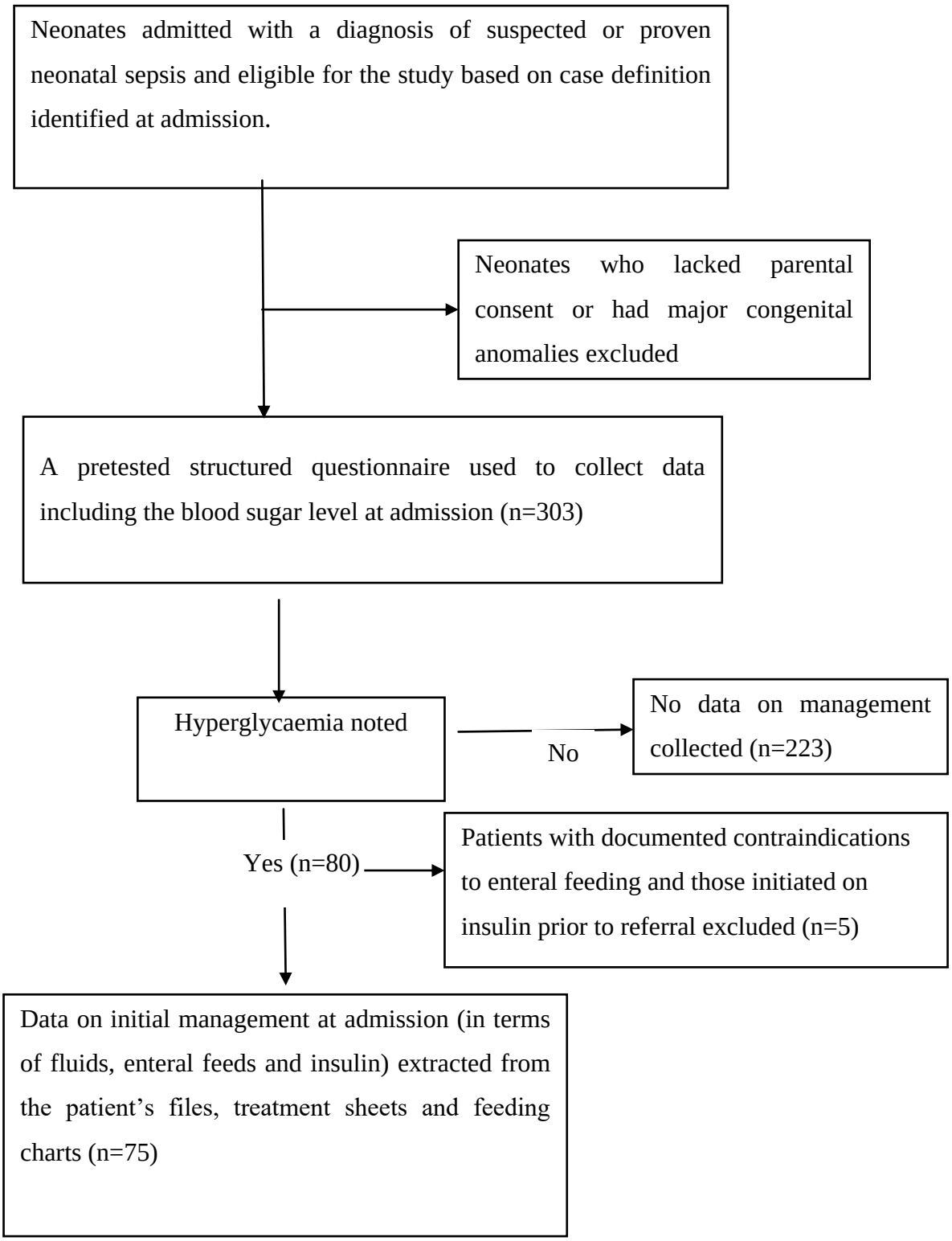
interviewing the mother or care giver. The Principal investigator or research assistants then examined the neonates. All the information collected was then recorded on the pretested questionnaire. The random blood sugar level which is routinely done for all sick neonates who are being admitted at the PEU or NBU, using the Accu Chek Active glucometers provided by the hospital, was then recorded. Findings of the total blood count (TBC) and the renal function tests which are also routinely done at admission were also recorded in the questionnaire.

Participants noted to be hyperglycemic had additional data on initial management, at admission, in terms of fluid management, enteral feeds and insulin collected from the participants' files, treatment sheets and feeding charts. Data collection on patient management was restricted to the participants who were hyperglycemic based on the case definition criteria. Data on management was also not be collected from neonates who had documented contraindications to enteral feeding such as coffee ground aspirates, apnoea and abdominal distention or had been initiated on insulin by a referring facility prior to presentation.

Outcomes of the neonates at the point of discharge (alive or dead) and duration of hospital admission was also noted.

Data were checked for completeness and accuracy on a daily basis and entered into a personal computer by the principal investigator using a Microsoft Excel data sheet.

Figure 1:Study procedure flow diagram



5.14 ACCU CHEK ACTIVE GLUCOMETER

Accu Chek Active glucometer is manufactured by Roche diagnostics. It uses reflectrometry technique in that the test strips contain a mutant variant of the enzyme glucose dehydrogenase which reacts with the glucose in the blood placed on the test strip and the subsequent chemical reaction generates a colour change on the test strip. The intensity of the colour depends on the glucose concentration. The meter then registers the colour change and converts it into a blood glucose value. The glucometer requires only 1-2 microliters of blood for testing and is plasma calibrated by the manufacturer to enable comparison of the blood glucose levels taken using the glucometer with serum glucose levels done in the laboratory. Accu Chek Active glucometer has been shown to meet the analytical and clinical quality requirements(65).The models available at KNH during the study period had also met the 2013 ISO standards for blood glucose meters(66).

Calibration is done before using the glucometer for the first time. This is done by inserting a black code chip found in the test strip box. The activation chip remains in the meter and can be used with all Accu Chek Active test strips. The newer model of Accu Chek Active Glucometer available in KNH does not require the code chip to be changed every time strips from a new test strip box are being used. Calibration and validation was done at the KNH biochemistry laboratory each time a new glucometer was issued during study period.

Quality Control

Quality control was done every morning, at the KNH biochemistry laboratory, during the period of the study. Quality control was done using a control solution provided by the manufacturer which was applied on the test pad of a test strip connected to the glucometer monitor and the reading displayed noted. The reading had to be within the stated range for the control solution. The range is indicated on the test strip box. If the reading was within the stated range a visual plausibility test was performed to confirm the performance of the glucometer. This was done by comparing the colour change noted on a round control window at the back of the test strip with a colour scale, with blood glucose values printed alongside it, found on the test strip container. If the colour on the control window of the strip matched the colour on the scale that corresponds to the value that had been read on the glucometer after application of the control solution, then the quality control was considered successfully and the glucometer was ready for use. Kenyatta National Hospital Biochemistry Laboratory is ISO certified.

5.15 DATA MANAGEMENT AND ANALYSIS

Data entered in the Microsoft Excel data sheet was exported to SPSS version 23 for analysis. Analysis was done using SPSS. Categorical data was tabulated and summarized as frequencies and proportions while continuous variables were reported as means with standard deviation or medians with interquartile ranges depending on the distribution.

The prevalence of hyperglycemia was computed as a proportion along with 95% confidence interval. Univariate associations of factors (independent variables) with hyperglycemia (dependent variable) was explored using chi square test (categorical data) and student's T-test (continuous variables). Associated factors were determined using multivariate logistic regression where odds ratio and 95% confidence intervals were calculated. A p value of <0.05 was considered significant.

Data on management were computed as frequencies and proportions.

5.16 CONTROL OF ERRORS AND BIAS

Quality control of the glucometers used during the study was done every morning at the KNH biochemistry laboratory.

The questionnaire was pretested, on a sample population not participating in the study, during the research assistants' training to assess how well formulated it was for complete data collection in terms of validity and reliability.

The research assistants were familiarized with the study and terms used in the questionnaire were explained to ensure uniform interpretation. The principal investigator assessed the information recorded in the questionnaire daily to ensure the validity of the collected data.

5.17 ETHICAL STATEMENT

Ethical approval was sought from University of Nairobi/Kenyatta National Hospital Ethics and Research Committee before commencing the study. The study was explained to the mother or caregiver of an eligible neonate and an informed written consent was obtained before recruitment into the study. No additional or preferential treatment was offered to the recruited subjects as an incentive to participate in the study. Emergency care or resuscitation was given priority over the research. Confidentiality of the study subjects was maintained.

6.0 RESULTS

A total of 303 neonates were recruited into the study.

Characteristics of the neonates admitted with a diagnosis of neonatal sepsis

The median age of the neonates was 9days (IQR 5- 16). There were 157 males (51.8%) with a male to female ratio of 1.1:1. Out of the 303 neonates, 292(96.2%) were delivered in a health facility out of whom 247/292 (86.4%) neonates had a birthweight of ≥2500g while 45/292 (15.4%) were low birth weight. Comparison of the birth weight and weight at admission showed that 169/292(57.8%) neonates had lost considerable weight with 32/169 (19.0%) having lost 10-15% of their birthweight and 67/169 neonates losing >15% of their birth weight. Neonates referred from other facilities were 201/303 (66.3%), while 33.7% were self- referral. The characteristics of the sample population are presented in table 3.

Table 3:N**eonatal characteristics**

	Frequency (n	**Percentage**
Age in days		
<7	99	32.7
7 – 14	120	39.6
15-21	58	19.1
22-28	26	8.6
Sex		
Male	157	51.8
Female	146	48.2
Gestational age		
<37 weeks	53	17.5
>37 weeks	250	82.5
Birth weight in g		
1500- 1999g	3	1.0
2000- 2499g	42	14.4
≥2500g	247	84.6
Mode of delivery		
SVD	219	72.3
CS	84	27.7
Place of delivery		
Home	7	2.3
Hospital	292	96.4
Born before arrival to hospital	4	1.3
Duration of rupture of membranes		
<12hrs	277	91.4
>12 hrs	26	8.6

Referred from another facility		
Yes	201	66.3
No (self-referral)	102	33.7
Percentage weight loss(n=169)		
<10%	70	41.4
10 -15%	32	19.0
>15%	67	39.6

Maternal Characteristics

The median age of the mothers was 27 years (IQR 23-30) with the youngest being 17 years and the oldest being 44 years. Majority of the mothers were married (84.2%) and multiparous (63%). Unemployed mothers were 143 out of the 303 (47.1%). Table 4 summarizes the maternal characteristics of the neonates who were recruited into the study.

Table 4: Maternal characteristics

	Frequency	Percentage
Age (years)		
<18	3	1.0
18 – 25	113	38.3
26 – 35	169	55.8
>35	18	5.9
Parity		
Primigravida	112	37.0
Multipara	191	63.0
Employment		
Homemaker	130	42.9
Informal	118	38.9
Formal	42	13.9
Unemployed	13	4.3
Marital status		
Married	255	84.2
Single	48	15.8
Level of education		
Primary	65	21.5
Secondary	148	48.8
Post-secondary	87	28.7
None	3	1.0

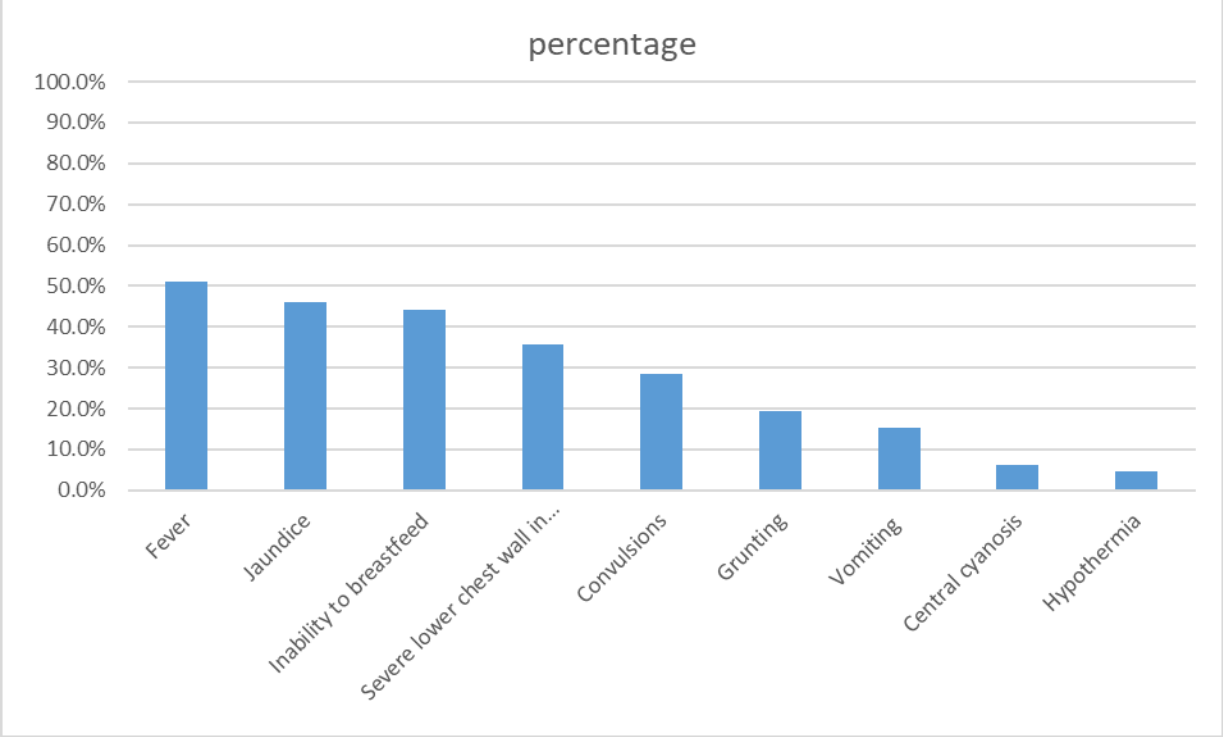
Clinical Characteristics of all the neonates who participated in the study

The median duration of illness was 3 days (IQR 2-6) with 177/303 neonates (57.8%)having a duration of illness of 1-3 days. The median creatinine level for the 303 neonates was 74 umol/l (IQR 42-126) and the median sodium level was 138 mmol/l (1QR 131-148). The clinical characteristics of the participants including laboratory evaluation are summarized in table 5 and figure 2.

Table 5: Clinical characteristics of the neonates including laboratory evaluation

	Frequency	**Percentage**
Duration of illness in days		
1	59	19.8
2- 3	118	38.9
>3	126	41.6
Temp (^{o}C)		
<35.5	14	4.6
35.5-37.5	134	44.2
>37.5	155	51.2
	Median	**IQR**
Median creatinine level (umol/l)	74	(42-126)
Median sodium levels (mmol/l)	138	(131-148.9)

Figure 2: Clinical characteristics of the neonates

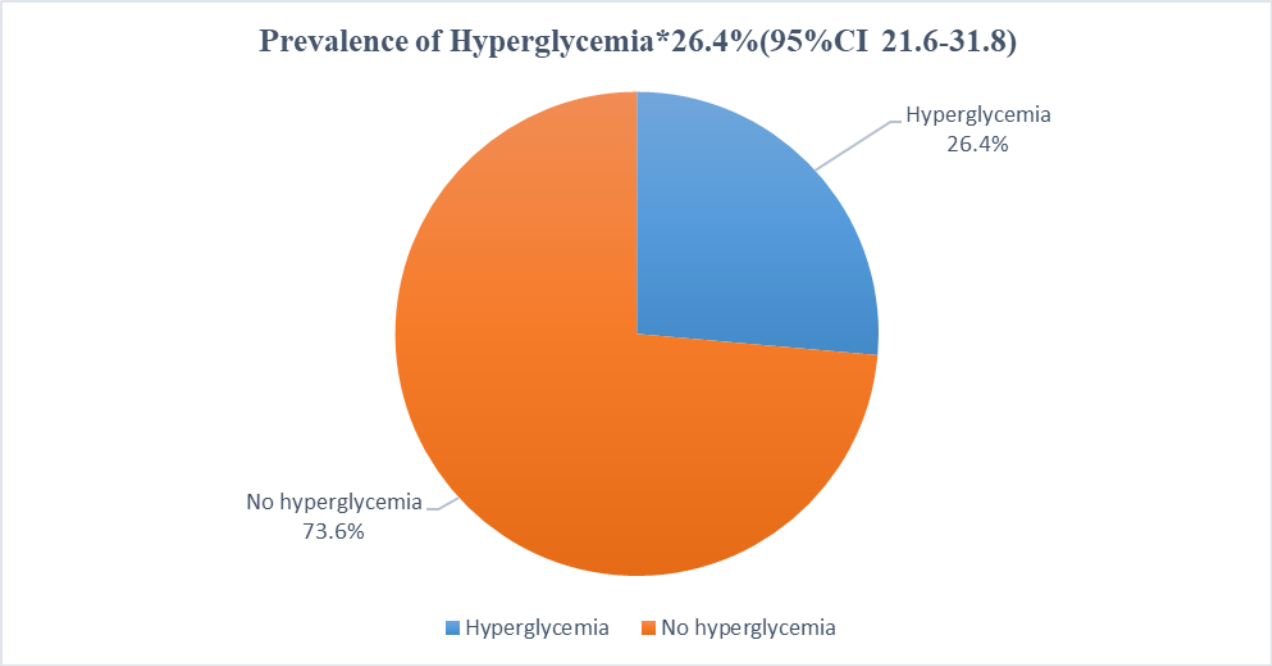


****The neonates could have presented with more than one clinical characteristic***

Hyperglycemia in neonates admitted with neonatal sepsis at KNH.

Eighty of all the 303 recruited neonates had hyperglycemia (plasma glucose level of >8.3mmol/l) giving a prevalence of **26.4% (95% CI 21.6- 31.8)**. The median plasma glucose level in the hyperglycemic group was 13.3mmol/l (IQR 9.75- 21.90) while the median plasma glucose for the whole study population was 5.1 (IQR 4.3- 8.5).

Figure 3: Prevalence of hyperglycemia in neonates admitted with neonatal sepsis at KNH.



**** Hyperglycemia – plasma glucose >8.3 mmol/l***

Association of hyperglycemia with neonatal characteristics

Univariate association of several neonatal characteristics with hyperglycemia was carried out and the characteristics summarized in table 6 were found to be statistically significant. Other characteristics such as sex of the neonate, gestational age, birth weight, mode of delivery, delivery at a health facility, rupture of membranes for > 12 hours, central cyanosis, vomiting, irritability and bulging anterior fontanelle were not found to be statistically significant**.**

Table 6: Neonatal characteristics significantly associated with hyperglycemia in neonatal sepsis

	Hyperglycemia				
	Yes n (%)	**No n (%)**	**Total n (%)**	**p-value**	**Odds ratio (95%CI)**
Age in days					
<7	18 (18.2)	81 (81.8)	99 (100)	0.026	**0.5 (0.3- 0.9)**
7 – 28	62 (30.4)	142 (69.6)	204(100)		
Referred from another health facility					
Yes	63 (31.3)	138 (68.7)	201 (100)	0.006	**2.3(1.3-4.1)**
No	17 (16.7)	85 (83.3)	102 (100)		
Dextrose administered prior to presentation to KNH					
Yes	32 (48.5)	34 (51.5)	66 (100)	0.001	**3.0 (1.6- 5.5)**
No	35 (24.0)	111 (76.0)	146 (100)		
Inability to breastfeed					
Yes	21 (15.7)	113 (84.3)	134(100)	<0.001	**0.3 (0.2- 0.6)**
No	59 (34.9)	110 (65.1)	169 (100)		
History of Convulsions					
Yes	37 (43)	49 (57)	86 (100)	<0.001	**3.0 (1.8- 5.3)**
Absent	43 (19.8)	174 (80.2)	217 (100)		
Temp <35.5 (^{0}C)					
Yes	8 (57.1)	6 (42.9)	14 (100)	0.023	**4.0(1.4- 12.0)**
No	72 (24.9))	217 (75.1)	289 (100)		
Jaundice					
Yes	28 (20.1)	111 (79.9)	139 (100)	0.026	**0.5 (0.3-0.91)**
No	52 (31.7)	112 (68.3)	164 (100)		
Severe lower chest wall in drawing					
Yes	42 (38.9)	66 (61.1)	108 (100)	<0.001	**2.6 (1.6-4.4)**
No	38 (19.5)	157 (80.5)	195 (100)		
Reduced movement/Floppy					
Yes	29 (40.3)	43 (59.7)	72(100)	0.003	**2.4 (1.4- 4.2)**
No	51 (22.1)	180 (77.9)	231 (100)		

Hyperglycemia in relation to laboratory evaluation

A high creatinine level was defined as > 130umol/l for neonates aged less than 7 days and > 70 umol/l in neonates more than 7 days of age. Thrombocytopenia was defined as platelet count of <150 $\times 10^9$/l while hypernatremia was defined as a sodium level of >150 mmol/l. Table 7 summarizes hyperglycemia in relation to the laboratory evaluation variables.

Table 7:Hyperglycemia in relation to laboratory evaluation

	Hyperglycemia				
	Yes	**No**	**Total**	**p-value**	**Odds ratio (95%CI)**
Thrombocytopenia					
Yes	39 (48.1)	42 (51.9)	81 (100)	<0.001	4.8 (2.7-8.5)
No	32 (16.3)	164 (83.7)	196 (100)		
Hypernatremia					
Yes	41 (61.2)	26 (38.8)	67 (100)	<0.001	7.8 (4.2-14.2)
No	38 (16.9)	187 (83.1)	225 (100)		
High creatinine levels for age					
Yes	57 (46.0)	67 (54.0)	124 (100)	<0.001	7.5(4.1- 13.9
No	17 (10.2)	150 (89.8)	167 (100)		

Hyperglycemia in neonatal sepsis in relation to maternal characteristics

Age ≤ 21 years was the only maternal characteristic significantly associated with hyperglycemia in neonatal sepsis as shown in table 8.

Table 8: Hyperglycemia in neonatal sepsis in relation to maternal characteristics

	Hyperglycemia				
	Yes	No	Total	P value	Odds ratio(CI 95%
Age (years)					
≤21	19 (39.6)	29 (60.4)	48 (100)	0.032	2.1 (1.1- 4.0)
>21	61 (23.9)	194 (76.1)	255 (100)		
Parity					
Primigravida	33 (29.5)	79 (70.5)	117 (100)	0.355	1.3 (0.8- 2.2)
Multipara	47 (24.6)	144 (75.4)	186 (100)		
Employment					
Unemployed	40 (28)	103 (72)	143 (100)	0.602	1.2 (0.7-2.0)
Employed	40 (25)	120 (75)	160 (100)		
Marital status					
Single	66 (25.9)	189 (74.1)	255 (100)	0.721	0.8 (0.4- 1.7)

Married	14 (29.2)	34 (70.8)	48 (100)		
Primary level of education or none					
Yes	21 (30.9)	47 (69.1)	68 (100)	0.352	1.3 (0.7- 2.4)
No	59 (25.1)	176 (74.9)	235 (100)		

Multivariate logistic regression analysis of association of hyperglycemia with other variables

In the multivariate analysis, we carried over neonatal, maternal and laboratory variables that were significantly associated with hyperglycemia on univariate analyses to a generalized linear model shown in table 9. Inability to breastfeed increased the odds of having hyperglycemia by 2.17[95%CI 1.05-4.46, p= 0.035]. Thrombocytopenia increased the odds of having hyperglycemia by 2.84[95%CI 1.40- 5.89, P= 0.004]while hypernatremia increased the odds of having hyperglycemia by 7.08[95%CI 3.38-14.85, p= <0.001]. Temperature of <35.5^{0}C increased the odds of having hyperglycemia in neonatal sepsis 5 fold [95%CI 0.90-32.02, p=0.046]

Table 9:Multivariate logistic regression of factors significantly associated with hyperglycemia in neonatal sepsis

	B	**S.E.**	**P value**	**OR**	**95% C.I. for OR**	
					Lower	**Upper**
Age of the neonates						
<7 days	-.043	.396	.913	.958	.441	2.080
7- 28 days (ref)				1		
Referred from facility (Yes)	.315	.395	.426	1.370	.631	2.973
Inability to breastfeed (Yes)	.774	.368	**.035**	**2.168**	**1.054**	**4.460**
Convulsions (Yes)	.515	.392	.189	1.673	.776	3.607
Temperature						
<35.5^{0}C	1.376	.827	**.046**	**4.959**	**0.903**	**32.023**
35.5^{0}C-37.5^{0}C (ref)				**1**		
Jaundice (Yes)	-.049	.372	.896	.952	.459	1.974
Severe lower chest in drawing (Yes)	.529	.356	.138	1.698	.844	3.413
Reduced movement (Yes)	.453	.390	.246	1.572	.732	3.378
Thrombocytopenia (Yes)	1.052	.367	**.004**	**2.864**	**1.395**	**5.877**
Hypernatremia (Yes)	1.958	.378	**.000**	**7.083**	**3.378**	**14.853**
High creatinine levels	.968	.488	.054	4.583	1.829	9.452
Maternal age						
≤21 years	.824	.454	.069	2.280	.937	5.550
>21years (ref)				1		

Management of hyperglycemia in neonatal sepsis.

Management was assessed for only the neonates who were found to be hyperglycemic. Data on management of hyperglycemia were analyzed for 75 out of the 80 neonates noted to be hyperglycemic after 5 neonates with documented contraindications to enteral feeding were excluded. The documented contraindications included coffee ground aspirates, apnea and distended abdomen**.** None of the neonates had been initiated on insulin by a referral facility at the time of admission.

Management in terms of enteral feeds, IV fluids and insulin.

Early initiation of enteral feeds is one of the recommended management of neonatal hyperglycemia and enteral feeds were prescribed, at admission, to only 43 out of the 75 eligible neonates (57.3%)**.** Breastmilk was the most commonly prescribed enteral feed. It was prescribed to 34/43(79.1%). neonates

The recommendations are that in a hyperglycemic neonate the dextrose infusion rate should not exceed 4-8 mg/kg/min and can even go lower. Dextrose containing intravenous (IV) fluids were prescribed for 39/59 (66.1%) neonates who had intravenous (IV) fluids prescribed at admission. The recommended amount of dextrose was prescribed for 29/39 (74.4 %) neonates with 8/39 (20.5%) neonates having 9-12mg/kg/min and 1/39 (5.1%) having >12mg/kg/min, which is beyond the maximum oxidative capacity for the neonates, prescribed**.**

Insulin was prescribed to 19/75 (25.3%) neonates at admission contrary to the recommendations that other measures such as decreasing the amount of dextrose and enteral feeding should be employed before insulin therapy**.** The mean blood glucose level at which dextrose was prescribed was 30.3mmol/l with the lowest blood glucose level being 15.4 mmol/l**.** Dosages of insulin that were above 0.05 units/kg (the recommended starting dose in neonates due to higher chances of hypoglycemia) were prescribed to 11/19 neonates (57.9%). Monitoring during insulin therapy was indicated for 15/19 (79.9%) neonates with 13/15 (80.7%) having the recommended frequency of at least every 1-2 hours. In our study12/19 (63.8%) neonates received intermittent glucose administration as opposed to the recommended continuous intravenous administration. Appropriate management as per the recommendations, in terms of all the three components (enteral feeding, amount of dextrose prescribed in IV fluids and insulin), was found in 33/75 (44%) neonates. Appropriate management was considered as enteral feeding being prescribed at admission for those who were eligible, amount of dextrose prescribed being below or within 4 - 8mg/kg/min for those

who had both Iv fluids and enteral feeds and no insulin at admission before the other measures of reducing blood glucose have been applied. The median blood glucose for the group that was appropriately managed was 9.8mmol/l (IQR 9.1-13.1) while the median blood glucose for those not appropriately managed was 19.7(IQR 13-29.5).

Table 10: Management of neonatal hyperglycemia

	Frequency (n =75)	**Percentage**
Enteral feeds prescribed at admission(yes)	43	57.3
IV (intravenous) fluids) prescribed at admission(yes)	59	78.7
Dextrose prescribed in IV fluids		
Yes	39	66.1
No	20	33.9
Amount of dextrose prescribed		
<4 mg/kg/min	6	15.4
4-8.9 mg/kg/min	23	58.9
9-12 mg/kg/min	8	20.5
>12mg/kg/min	2	5.1
Insulin prescribed at admission		
Yes	19	25.3
No	56	74.7
Mode of administration of insulin		
Intermittent/stat	12	63.8
Continuous Infusion	7	38.2
Dosage in U/kg/hour for infusion		
0.025- 0.05	5	41.7
0.06-0.1	7	58.3
Dosage in U/kg for intermittent/stat		
0.025- 0.05	3	42.9
0.06- 0.1	3	42.9
>0.1	1	14.3
Blood glucose monitoring during insulin therapy ordered		
Yes	15	79.9
No	4	21.1
Frequency of blood glucose monitoring during insulin therapy ordered		
hourly	10	66.7
Two hourly	3	20.0
>2 hourly	2	13.3

Overall appropriate management in terms of enteral feeds, insulin and amount of dextrose prescribed in IV fluids		
Yes	33	44
No	42	56

Outcome, in terms of mortality, of all the neonates with sepsis recruited in the study at the point of discharge.

Out of the all 303 neonates with sepsis who made up the study population, 254 (83.8%) were alive at the time of discharge with 49/303 (16.2%) having died in the course of their hospital stay. Hyperglycemia was significantly associated with mortality with the odds of having hyperglycemia being increased in the neonates who died OR 5.7 (95% CI 3.0- 11.0) and p= <0.001. Out of the 49 neonates with sepsis who died 29 (59.2%) had hyperglycemia.

Table 11:Hyperglycemia in relation to outcome in terms of mortality.

	Dead				
	Yes	**No**	**Total**	**P value**	**Odds ratio(CI 95%)**
Hyperglycemia	29 (36.3)	51 (63.7)	80 (100)	<0.001	5.7(3.0-11.0)
No hyperglycemia	20 (9.0)	203 (91.0)	223 (100)		

7.0 DISCUSSION

This study aimed to determine the prevalence, associated factors and management of hyperglycemia in neonates admitted to KNH with a diagnosis of suspected or proven neonatal sepsis. Hyperglycemia was defined as plasma glucose level > 8.3 mmol/l and the prevalence of hyperglycemia, at admission, in neonates admitted with sepsis was found to be 26.4% (95%CI 21.6- 31.8). There is limited research on hyperglycemia in neonatal sepsis and the global prevalence is unknown. There is also no global consensus on the definition of neonatal hyperglycemia and this has made comparison of studies difficult due to the different cut offs used.

The prevalence of hyperglycemia found in our study was comparable to that of a similar study done in Kenya by Njihia *et al* that found the prevalence of hyperglycemia in neonates admitted with sepsis at Kisii Level 5 Hospital to be 23%(19).The comparability could be due to the fact that the study used a similar study design and a similar cut off for the plasma glucose level. However, the highest plasma glucose recorded in the study by Njihia *et al* was 10.7mmol/l compared to our study that had 6 neonates with blood glucose levels of >33.3mol/l. This could be attributed to the larger sample size and the fact that KNH is a national referral hospital receiving most of the severe cases of neonatal sepsis. A prospective analytical study by Ahmad *et al* done in Pakistan, using a blood glucose level cut off of 11.1 mmol/l, found the prevalence of hyperglycemia in 502 neonates with suspected or confirmed neonatal sepsis to be at 6.9%(28). The lower prevalence can be attributed to the higher blood glucose cut off used. A retrospective analysis of 75 years' data on neonatal sepsis with positive blood culture at Yale New Haven Hospital found that hyperglycemia was present in 32.1% of all cases(26). Hyperglycemia was defined as blood glucose level >7.8 mmol/l and the higher prevalence could be due to a lower blood glucose level and a definitive diagnosis of neonatal sepsis. A prospective observational study on glycemic status and its effect on neonatal sepsis done in Bangladesh by Islam. *et al* used a plasma glucose level cut off of >145mg/dl (8.1mg/dl) and found that the prevalence of hyperglycemia was 15.3%(27). The lower prevalence is possibly due the fact that blood glucose level was only done for the neonates with a positive blood culture and CRP.

Our study also found that a significant association between hyperglycemia and mortality with the odds of having hyperglycemia being increased in the neonates who died, OR 5.7 (95%CI 3.0-11.0) and p=<0.001. This is comparable to the study by Ahmad et al in Pakistan that sought to deternine the blood glucose levels in neonatal sepsis and its association with mortality. They found that a

blood glucose level >11.1 mmol/l was significantly associated with mortality (p<0.05)and a study by Islam et al in Bangladesh (p<0.001) that found that mortality was significantly higher in septic newborns with hyperglycemia(27,28).

Though inability to breastfeed has been regarded to imply hypoglycemia in many studies, in this study it was significantly associated with hyperglycemia and increased the odds of getting hyperglycemia in neonates with sepsis [OR 2.17(95%CI 1.04- 4.46) and p= 0.035]. This could be due to the fact that enteral feeding has been shown to promote better control of blood glucose levels in neonates since it stimulates the enteroendocrine cells to produce incretin hormones that stimulate insulin production from the pancreatic cells(55,56). This is supported by a cross sectional comparative study in Egypt done by Akmal *et al* that showed a statistically significant association of hyperglycemia with less milk intake (p= 0.007)(30). A study by Yoon *et al* also showed that hyperglycemia was less common in the first 24 hours in neonates who were started on enteral feeds (OR 0.162, P= 0.01)(31). A study by Grimaud *et al* also found that enteral route of glucose was associated with a lower number of hyperglycemic neonates (p=0.04)(67). This was contrary to the study by Njihia *et al* that did not find significant association between inability to breastfeed and hyperglycemia in neonatal sepsis.

Our study also found a significant association between hypernatremia and hyperglycemia, OR 7.3 (95%CI 3.9-13.4) and p=<0.001. Hyperglycemia can be associated with hypernatremia though the exact mechanism is unknown but the stress caused by hypovolemia in hypernatremia has been implicated(68). . Thrombocytopenia increased the odds of getting hyperglycemia, OR 2.87 (95%CI 1.40- 5.88) and p= 0.004. This could be explained by the fact that thrombocytopenia is one of the haematological changes that can occur in severe sepsis as a result of disseminated intravascular coagulopathy (DIC) which is a complication of neonatal sepsis. A significant association was also found between hypothermia (temperature <35.5^{0}C) and neonatal hyperglycemia in this study, OR 4.959 (95%CI 0.903-32.023) and p= 0.046. There are no studies associating hyperglycemia in neonatal sepsis with hypothermia. The significant association of hyperglycemia with inability to breastfeed, hypothermia and thrombocytopenia could also be due to the fact that these variables occur in severe forms of sepsis. The stress and inflammation that occur in sepsis lead to an increase in the counter regulatory hormones that in turn lead to hyperglycemia. Hypernatremia can also occur as a result of inability to breastfeed and the dehydration associated with it results in stress that could lead to hyperglycemia through the same mechanism.

Most of the studies assessing management of neonatal hyperglycemia have been done on premature and LBW infants. There is currently no international consensus on the optimal management but

practice is improving as neonatal units develop local guidelines on the basis of limited available research(20). At the time of the study there were no locally adapted guidelines but the Kenya National Neonatal Guidelines for Hospitals, containing a section on management of neonatal hyperglycemia, was launched in November 2018 and by the end of the study period dissemination had not been done. The recommendations of the guidelines are in keeping with the various recommendations from different parts of the world. There was variability of care in regard to the amount of dextrose prescribed in intravenous fluids, initiation of enteral feeds to those who were eligible and use of insulin which likely reflects the lack of published guidelines at the time of the study. This is comparable to the findings of a survey by Alsweiler *et al* in Australasia and a survey of management of neonatal hyperglycemia in level 3 neonatal units in UK by Gupta *et al* that showed variability of care between the various units(20,51).

The study in Australasia found that 70% of the respondents would decrease glucose intake as opposed to giving insulin as the first response while 30% would start insulin as their first response. This is comparable to our study that found that 26.4% of the neonates had insulin prescribed during the initial management at admission.

Study Limitations

The study relied on a single blood glucose reading taken by the health care workers at KNH while the recommendations are that hyperglycemia should be confirmed by a second reading in the laboratory.

Data on management of hyperglycemia was collected from the patients records and it was assumed that what was recorded is what was actually done.

The initial diagnosis of neonatal sepsis was made by the admitting resident doctor and the accuracy may have affected the results.

Diagnosis was suspected and thus not comparable with studies where labs were used.

8.0 CONCLUSIONS

The prevalence of hyperglycemia, at admission, in neonates admitted to KNH with a diagnosis of neonatal sepsis was found to be 26.4%. Inability to breastfeed, hypernatremia, thrombocytopenia and a temperature of <35.5 ^{0}C were significantly associated with hyperglycemia. Appropriate management as per the recommendations (in terms of all the three components combined) was found in only 33/75 (44%) neonates with the largest gaps in the management being in the initiation of enteral feeds for the eligible neonates and insulin, in terms of the dosage prescribed and mode of administration.

9.0 RECOMMENDATIONS

- Neonates with suspected sepsis and inability to breastfeed should be actively screened for hyperglycemia and those with sepsis and hyperglycemia should be screened for thrombocytopenia and hypernatremia.
- Owing to the gaps in management there is need for dissemination and implementation of the neonatal guidelines considering the significant association between hyperglycemia in neonatal sepsis and mortality.

REFERENCES

1. UNICEF. Levels and Trends in Child_Mortality_Report_2017.pdf. Available from: https://www.unicef.org/publications/files/Child_Mortality_Report_2017.pdf

2. UNICEF. Maternal and Child Health disparities, Kenya: country profile_KEN.pdf. Available from: https://data.unicef.org/wp-content/uploads/country_profiles/Kenya/country%20profile_KEN.pdf

3. Kenya National Bureau of Statistics. ICF Macro. Kenya Demographic Health Survey 2014.pdf. Available from: https//dhsprogram.com/pubs/pdf/fr308.pdf...

4. Márquez-González H, Muñoz-Ramírez MC, Ramírez-García MA, Pineda-Frutos MF, Hernández-Ramírez C, Villa-Romero AR, et al. [Hyperglycemia as a risk factor for mortality in critically ill neonates]. Rev Medica Inst Mex Seguro Soc. 2014;52 Suppl 2: S104—9.

5. Egi M, Bellomo R, Stachowski E, French CJ, Hart G. Variability of Blood Glucose Concentration and Short-term Mortality in Critically Ill Patients. Anesthesiol J Am Soc Anesthesiol. 2006 Aug 1;105(2):244–52.

6. Hays SP, Smith EO, Sunehag AL. Hyperglycemia Is a Risk Factor for Early Death and Morbidity in Extremely Low Birth-Weight Infants. Pediatrics. 2006 Nov 1;118(5):1811–8.

7. Ali NA, O'Brien JM, Jr, Dungan K, Phillips G, Marsh CB, et al. Glucose variability and mortality in patients with sepsis. Crit Care Med. 2008 Aug;36(8):2316.

8. Auerbach A, Eventov-Friedman S, Arad I, Peleg O, Bdolah-Abram T, Bar-Oz B, et al. Long Duration of Hyperglycemia in the First 96 Hours of Life Is Associated with Severe Intraventricular Hemorrhage in Preterm Infants. J Pediatr. 2013 Aug 1;163(2):388–93.

9. Mohamed S, Murray JC, Dagle JM, Colaizy T. Hyperglycemia as a risk factor for the development of retinopathy of prematurity. BMC Pediatr. 2013; 13:78.

10. Kaempf JW, Kaempf AJ, Wu Y, Stawarz M, Niemeyer J, Grunkemeier G. Hyperglycemia, insulin and slower growth velocity may increase the risk of retinopathy of prematurity. J Perinatol. 2011 Apr;31(4):251.

11. Zadeh VB, Khademi G, Rakhshanizadeh F, Imani B, Abdollahpour N, Sezavar M. Impact of Hyperglycemia Duration on Mortality and Ventilator Dependence in Neonatal Intensive Care Unit. Iran J Neonatol. 2017 Jun 1;8(2):36–43.

12. Arsenault D, Brenn M, Kim S, Gura K, Compher C, Simpser E, et al. A.S.P.E.N. Clinical Guidelines. J Parenter Enter Nutr. 2012 Jan 1;36(1):81–95.

13. MW SA and H. Glucose extremes in newborn infants. - PubMed - NCBI [Internet]. [cited 2018 Apr 24]. Available from: http://login.research4life.org/tacsgr1www_ncbi_nlm_nih_gov/pubmed/12168240

14. Hey E. Hyperglycaemia and the very preterm baby. Semin Fetal Neonatal Med. 2005 Aug 1;10(4):377–87.

15. Decaro MH, Vain NE. Hyperglycaemia in preterm neonates: What to know, what to do. Early Hum Dev. 2011 Mar;87:S19–22.

16. Yeung Melinda Y. Glucose intolerance and insulin resistance in extremely premature newborns, and implications for nutritional management. Acta Paediatr. 2007 Mar 29;95(12):1540–7.

17. Ogilvy-Stuart AL, Beardsall K. Management of hyperglycaemia in the preterm infant. Arch Dis Child - Fetal Neonatal Ed. 2010 Mar 1;95(2): F126–31.

18. Rozance PJ, Hay WW. Neonatal Hyperglycemia. NeoReviews. 2010 Nov 1;11(11): e632–9.

19. Njihia GW. Prevalence of hyperglycemia and associated risk factors in neonates with sepsis at Kisii level five hospital [Internet] [Thesis]. University of Nairobi; 2014 [cited 2018 May 1]. Available from: http://erepository.uonbi.ac.ke:8080/xmlui/handle/11295/77554

20. Gupta A, Lakshmanan A, Harikumar C, Janakiraman S. 1352 Survey of Management of Neonatal Hyperglycaemia in Level 3 Neonatal Units in UK. Arch Dis Child. 2012 Oct 1;97(Suppl 2): A385–A385.

21. WHO reviews. Antibiotic Use for Sepsis in Neonates and Children: 2016 Evidence Update. Available from:http://www.who.int/selection_medicines/committees/expert/21/applications/s6_paed_antibiotics_appendix4_sepsis.pdf

22. Young Infants Clinical Signs Study Group. Clinical signs that predict severe illness in children under age 2 months: a multicentre study. Lancet Lond Engl. 2008 Jan 12;371(9607):135–42.

23. Opiyo N, English M. What clinical signs best identify severe illness in young infants aged 0–59 days in developing countries? A systematic review. Arch Dis Child. 2011 Nov 1;96(11):1052–9.

24. European Medicines Agency. Report on the expert meeting on neonatal and paediatric sepsis. Available from: http://www.ema.europa.eu/docs/en_GB/document_library/Report/2010/12/WC500100199.pdf

25. Soghier LM, Brion LP. Multivariate analysis of hyperglycemia in extremely low birth weight infants. J Perinatol. 2006 Dec;26(12):723.

26. Bizzarro MJ, Raskind C, Baltimore RS, Gallagher PG. Seventy-Five Years of Neonatal Sepsis at Yale: 1928–2003. Pediatrics. 2005 Sep 1;116(3):595–602.

27. Islam MS, Mia MAH, Akhter KR, Haque M, Malik MA. Glycemic Status and its Effect in Neonatal Sepsis in a Tertiary Care Hospital. Bangladesh J Child Health. 2017 Feb 13;40(1):21–5.

28. Ahmad S, Khalid R. Blood Glucose Levels in Neonatal Sepsis and Probable Sepsis and its Association with Mortality. J Coll Physicians Surg--Pak JCPSP. 2012 Jan 1; 22:15–8.

29. Mohammed MM, Rahman SMA. Frequency of neonatal hyperglycaemia at Gaafar Ibnauf Children's Hospital: Clinical aspects and short term outcome. Sudan J Paediatr. 2016;16(1):45.

30. Akmal DM, Razek ARAA, Musa N, El-Aziz AGA. Incidence, risk factors and complications of hyperglycemia in very low birth weight infants. Egypt Pediatr Assoc Gaz. 2017 Sep 1;65(3):72–9.

31. Yoon JY, Chung HR, Choi CW, Yang SW, Kim BI, Shin CH. Blood glucose levels within 7 days after birth in preterm infants according to gestational age. Ann Pediatr Endocrinol Metab. 2015 Dec;20(4):213–9.

32. Beardsall K, Vanhaesebrouck S, Ogilvy-Stuart AL, Vanhole C, Palmer CR, Ong K, et al. Prevalence and determinants of hyperglycemia in very low birth weight infants: cohort analyses of the NIRTURE study. J Pediatr. 2010 Nov;157(5):715-719.e1-3.

33. Soghier LM, Brion LP. Multivariate analysis of hyperglycemia in extremely low birth weight infants. J Perinatol Off J Calif Perinat Assoc. 2006 Dec;26(12):723–5.

34. Polin RA, Fox WW, Abman SH. Fetal and Neonatal Physiology: Expert Consult - Online and Print. Elsevier Health Sciences; 2011. 2213 p.

35. Hume R, Burchell A, Williams FLR, Koh DKM. Glucose homeostasis in the newborn. Early Hum Dev. 2005 Jan 1;81(1):95–101.

36. Cowett RM, Farrag HM. Selected principles of perinatal–neonatal glucose metabolism. Semin Neonatol. 2004 Feb 1;9(1):37–47.

37. Mueckler M, Thorens B. The SLC2 (GLUT) Family of Membrane Transporters. Mol Aspects Med. 2013;34(0):121–38.

38. Marik PE, Raghavan M. Stress-hyperglycemia, insulin and immunomodulation in sepsis. Intensive Care Med. 2004 May 1;30(5):748–56.

39. Beardsall K, Yuen K, Williams R, Dunger D. Applied physiology of glucose control. Curr Paediatr. 2003 Dec 1;13(7):543–8.

40. Gleason CA, Juul SE, editors. Avery's diseases of the newborn [Internet]. Tenth edition. Philadelphia, PA: Elsevier; 2018. Available from: https://www-clinicalkey-com.access.library.miami.edu/#!/browse/book/3-s2.0-C20130003209

41. Quesada I, Tudurí E, Ripoll C, Nadal Á. Physiology of the pancreatic α-cell and glucagon secretion: role in glucose homeostasis and diabetes. J Endocrinol. 2008 Oct 1;199(1):5–19.

42. Osier F, Berkley J, Ross A, Sanderson F, Mohammed S, Newton C. Abnormal blood glucose concentrations on admission to a rural Kenyan district hospital: prevalence and outcome. Arch Dis Child. 2003 Jul;88(7):621.

43. Vanhorebeek I, Gunst J, Berghe GV den. Critical Care Management of Stress-Induced Hyperglycemia. Curr Diab Rep. 2018 Apr 1;18(4):17.

44. Marik PE, Bellomo R. Stress hyperglycemia: an essential survival response! Crit Care. 2013;17(2):305.

45. Devaskar SU, Garg M. Disorders of Carbohydrate Metabolism in the Neonate. In: Fanaroff and Martin's Neonatal-Perinatal Medicine [Internet]. 10th ed. Philadelphia, PA: Elsevier/Saunders; 2015. p. 1434–59. Available from: https://www-clinicalkey-com.access.library.miami.edu/#!/content/book/3-s2.0-B9781455756179000956

46. Doyle LW, Cheong JL, Ehrenkranz RA, Halliday HL. Late (> 7 days) systemic postnatal corticosteroids for prevention of bronchopulmonary dysplasia in preterm infants. In: The Cochrane Library [Internet]. John Wiley & Sons, Ltd; 2017 [cited 2018 Jun 5]. Available from: http://cochranelibrary-wiley.com/doi/10.1002/14651858.CD001145.pub4/full

47. Ministry of Health, Kenya. Basic Paediatric Protocols 2016.pdf.Available from idoc-africa.org.

48. Akech S, Rotich B, Chepkirui M, Ayieko P, Irimu G, English M. The Prevalence and Management of Dehydration amongst Neonatal Admissions to General Paediatric Wards in Kenya—A Clinical Audit. J Trop Pediatr [Internet]. [cited 2018 Aug 8]; Available from: https://academic.oup.com/tropej/advance-article/doi/10.1093/tropej/fmx108/4796876

49. Mohamed S, Murray JC, Dagle JM, Colaizy T. Hyperglycemia as a risk factor for the development of retinopathy of prematurity. BMC Pediatr. 2013;13:78.

50. Alaedeen DI, Walsh MC, Chwals WJ. Total parenteral nutrition–associated hyperglycemia correlates with prolonged mechanical ventilation and hospital stay in septic infants. J Pediatr Surg. 2006 Jan 1;41(1):239–44.

51. Alsweiler JM, Kuschel CA, Bloomfield FH. Survey of the management of neonatal hyperglycaemia in Australasia. J Paediatr Child Health. 2007 Sep 1;43(9):632–5.

52. Bottino M, Cowett RM, Sinclair JC. Interventions for treatment of neonatal hyperglycemia in very low birth weight infants. In: The Cochrane Library [Internet]. John Wiley & Sons, Ltd; 2011 [cited 2018 Mar 13]. Available from: http://onlinelibrary.wiley.com/doi/10.1002/14651858.CD007453.pub3/full

53. Werny D, Taplin C, Bennett JT, Pihoker C. Disorders of Carbohydrate Metabolism. In: Avery's Diseases of the Newborn [Internet]. 10th ed. Philadelphia, PA: Elsevier; 2018. p. 1403–1416.e3. Available from: https://www-clinicalkey-com.access.library.miami.edu/#!/content/book/3-s2.0-B9780323401395000991?scrollTo=%23hl0001077

54. Hawdon J, Cheetham T, Schenk DJ, Wraith JE, Jones SA, Bishop N. Metabolic and endocrine disorders. In: Rennie and Roberton's Textbook of Neonatology [Internet]. 5th ed. Philadelphia, PA; 2012. p. 849–926. Available from: https://www-clinicalkey-com.access.library.miami.edu/#!/content/book/3-s2.0-B9780702034794000350?scrollTo=%23hl0002362

55. Drucker DJ. The role of gut hormones in glucose homeostasis. J Clin Invest. 2007 Jan 2;117(1):24–32.

56. Leech CA, Dzhura I, Chepurny OG, Kang G, Schwede F, Genieser H-G, et al. Molecular physiology of glucagon-like peptide-1 insulin secretagogue action in pancreatic β cells. Prog Biophys Mol Biol. 2011 Nov 1;107(2):236–47.

57. Salis ER, Reith DM, Wheeler BJ, Broadbent RS, Medlicott NJ. Insulin resistance, glucagon-like peptide-1 and factors influencing glucose homeostasis in neonates. Arch Dis Child - Fetal Neonatal Ed. 2017 Mar 1;102(2): F162–6.

58. Beardsall K, Vanhaesebrouck S, Ogilvy-Stuart AL, Vanhole C, Palmer CR, van Weissenbruch M, et al. Early Insulin Therapy in Very-Low-Birth-Weight Infants [Internet]. http://dx.doi.org/10.1056/NEJMoa0803725. 2009 [cited 2018 Mar 21]. Available from: http://www.nejm.org/doi/full/10.1056/NEJMoa0803725

59. Alsweiler JM, Harding JE, Bloomfield FH. Tight Glycemic Control with Insulin in Hyperglycemic Preterm Babies: A Randomized Controlled Trial. Pediatrics. 2012 Apr 1;129(4):639–47.

60. Verbruggen SC, Landzaat LJ, Reiss IKM, Goudoever JB van, Joosten KFM. Efficacy and Safety of a Tight Glucose Control Protocol in Critically Ill Term Neonates. Neonatology. 2012;101(3):232–8.

61. Hertz DE. Care of the Newborn: A Handbook for Primary Care [Internet]. Philadelphia, UNITED STATES: Wolters Kluwer Health; 2005. Available from: http://ebookcentral.proquest.com/lib/miami/detail.action?docID=2032468

62. SLHD Royal Prince Alfred Hospital - Newborn Care - Medical Guidelines [Internet]. [cited 2018 Mar 21]. Available from: https://www.slhd.nsw.gov.au/rpa/neonatal/protocols.html

63. Insulin_for_hyperglycaemia_Neomedv1.2_full_20170620.pdf [Internet]. [cited 2018 Apr 30]. Available from: https://www.slhd.nsw.gov.au/RPA/neonatal%5Ccontent/pdf/Medications_Neomed/Insulin_for_hyperglycaemia_Neomedv1.2_full_20170620.pdf

64. Andrew Fisher Et al. Handbook for family planning operations research design. 2nd ed. | POPLINE.org [Internet]. [cited 2019 Jun 3]. Available from: https://www.popline.org/node/317104

65. Dhatt GS, Agarwal MM, Othman Y, Nair SC. Performance of the Roche Accu-Chek Active Glucose Meter to Screen for Gestational Diabetes Mellitus Using Fasting Capillary Blood. Diabetes Technol Ther. 2011 Aug 24;13(12):1229–33.

66. ISO Standards for Blood Glucose Meters and Test Strips [Internet]. [cited 2018 Jun 7]. Available from: https://www.diabetes.co.uk/blood-glucose-meters/iso-accuracy-standards.html

67. Grimaud M, de Lonlay P, Dupic L, Arnoux J-B, Brassier A, Hubert P, et al. High glucose intake and glycaemic level in critically ill neonates with inherited metabolic disorders of intoxication. Eur J Pediatr. 2016 Jun 1;175(6):849–58.

68. Boskabadi H, Rakhshanizadeh F. Neonatal Hypernatremic Dehydration and Thrombocytopenia: Its Prevalence and Relationship with Prognosis. Iran J Pediatr [Internet]. 2018 Aug [cited 2019 May 5];28(4). Available from: http://ijp.tums.pub/en/articles/65742.html

APPENDIX I: INFORMED CONSENT FORM

Patient's Study Identification Number:

Date:

Title: PREVALENCE, ASSOCIATED FACTORS AND MANAGEMENT OF HYPERGLYCEMIA IN NEONATES ADMITTED WITH NEONATAL SEPSIS AT KENYATTA NATIONAL HOSPITAL

Investigator: Dr Emelda Manguro

Tel No: 0724360873

Investigator's Statement:

We are requesting you and your child to kindly participate in this research study. The purpose of this consent explanation form is to provide you with the information you will need to help you decide whether to participate in the study or not. Please read this consent information carefully and ask any questions or seek clarification on any matter concerning the study.

Introduction:

Neonatal sepsis is a condition that occurs because of infection (mostly bacterial) of the blood of a newborn. The normal functioning of the body is disrupted as the body tries to deal with the infection and one of the abnormalities that can occur is high blood glucose levels. High blood glucose in a newborn can cause problems such as dehydration, electrolyte imbalance, reduced ability to fight infections and bleeding into the brain which can lead to death. The glucose level is determined by measuring the blood of the baby. This study aims to find out how common high blood glucose levels occur in sick newborns, factors associated with it and how it is being managed with an aim of providing information that will assist in improving care.

Procedures

If you agree to participate in the study, you will be required to answer a set of questions about yourself and your child. No additional tests or procedures will be done during the study. The only procedures done during the study are those offered in the routine care of your child. This will include the random blood sugar level, kidney function tests and total blood count which is routinely measured in newborns being admitted to our facility and will not harm your child.

Benefits:

The information from the study will help in knowing the magnitude of the problem and may be used to improve care of the newborns hence increase survival.

Risks:

There will be no risks to you or your child during the study. There will be no invasive procedures carried out in the study. Refusal to participate will in no way affect the treatment of your child.

Voluntariness:

The study will be fully voluntary. There will be no financial rewards to you for participating in the study. One is free to participate or withdraw from the study at any point. Refusal to participate will not compromise your child's management in any way.

Confidentiality:

The information obtained about you, your child and your family will be kept in strict confidence. No specific information regarding you, your child or your family will be released to any person without your written permission. We will, however, discuss general overall findings regarding all children assessed but nothing specific will be discussed regarding you or your child. We will also, not reveal the identity of you or your child in these discussions.

Problems or Questions:

If you ever have any questions about the study or about the use of the results you can contact the principal investigator on the contacts provided

If you have any questions on your rights as a research participant, you can contact the **Kenyatta National Hospital Ethics and Research Committee (KNH- ESRC)** by calling **2726300 Ext. 44355**

I _____do confirm that I have read/ been explained to the above study, understood the information presented to me and have had the opportunity to ask questions. I understand that my participation is voluntary and that I am free to withdraw from this study at any time without giving reason. I agree to take part out of my own free will and no coercion or incentive has been offered.

Signature of participant_____ Date: _____

I _____ declare that I have adequately explained to the above participant, the study procedure, risks, and benefits and given him /her time to ask questions and seek clarification regarding the study. I have answered all the questions raised to the best of my ability.

Interviewers Signature _____Date _____

APPENDIX II: FOMU YA KUPATA IDHINI LA WAZAZI/WALEZI WA WASHIRIKA

UTAFITI WA UFANISI WA TATIZO LA VIWANGO VYA JUU YA SUKARI MWILINI KWA WATOTO WAGONJWA WALIO CHINI YA MWEZI MMOJA WAKATI WANALAZWA KATIKA HOSPITALI YA KENYATTA, SABABU ZINAZOHUSIANA NA HALI HII NA TARATIBU ZINAZOFUATWA KATIKA KUTIBU HALI HII.

Mchunguzi Mkuu: Dr. Emelda Manguro

Nambari ya Simu: 0724360873

Taarifa la Wachunguzi

Tunakualika pamoja na mtoto wako kushiriki katika utafiti huu. Sababu ya fomu hii ni kukupa maelezo zaidi juu ya utafiti huu ili uweze kuamua kama wewe na mtoto wako mtahushishwa au la. Tafadhali soma maelezo kwa makini na ukiwa na maswali yoyote jiskie huru kuuliza.

Lengo la utafiti

Lengo la utafiti huu ni kuonyesha idadi ya watoto wagonjwa walio chini ya mwezi mmoja wanaopatikana na tatizo la viwango vya juu ya sukari mwilini wakati wanapolazwa hospitalini, sababu zinazohusiana na hali hii na taratibu zinazofuatwa kutibu hali hii. Maelezo kutoka utafiti huu itasaidia kuboresha matibabu ya hawa watoto.

Faida:

Matokeo ya utafiti huu itasaidia kuboresha matibabu ya hawa watoto.Itasaidia wahudumu wa afya pia kuamua kama wanahitaji kubuni sera za kupambana na tatizo hili.

Hatari:

Hakutakuwa na hatari lolote litakalomkumba mtoto wako wakati wa utafiti..Hakuna vipimo vya ziada vihitajika katika utafiti huu. Taratibu na Vipimo ambavyoo vitachunguzwa katika utafiti huu ni vile vinafanywa kwa kawaida kwa watoto wote wagonjwa wakati wanalazwa hospitalini.Kwa mfano kipimo cha kiwango cha sukari kitakachoangaliwa ni kile kitapimwa wakati mtoto analazwa hospitalini

Kujitolea:

Kushiriki katika huu utafiti ni kwa hiari yako. Hakutakuwa na faida lolote la kifedha. Una uhuru wa kukataa kushiriki na kukataa kwako hakutatumiwa kukunyima tiba.

Siri:

Chochote utakachotueleza kuhusu mtoto wako au wewe yatakuwa siri na matokeo ya utafiti yataelezwa kwa ujumla.

Maswali

Ukiwa na maswali au tatizo lolote kuhusu utafiti huu, kuwa huru kuwasiliana na mtafiti mkuu Daktari Emelda Manguro kupitia nambari ya simu 0724-360873.

Ukiwa na swali kuhusu haki zako katika utafiti huu au unahisi kuwa haki zako zimekeukwa unaweza kuwasiliana na mwenyekiti wa kamati ya **Kenyatta National Hospital Ethics and Research Committee (KNH- ESRC)** kupitia nambari ya simu 020-2726300, Ext. 44355**.**

Mimi_____nimepewa maelezo ya kutosha kuhusu utafiti huu na nina kubali kuhusishwa katika utafiti huu.

Idhini ya mlezi: _____ Tarehe_____

Mimi_____nimempa mzazi/ mlezi wa mshiriki wa utafiti huu maelezo kamili kuhusiana na utafiti huu na kujibu maswali yote aliyouliza.

Sahihi la mchunguzi _____Tarehe_____

APPENDIX III*:* SCREENING TOOL FOR SUSPECTED NEONATAL SEPSIS.

(adapted from WHO IMCI guidelines and Ministry of Health Basic Paediatric Protocols)

Tick as appropriate (consider suspected neonatal sepsis is ONE or MORE of the following)

- Bulging fontanelle
- Change in level of activity
- Cyanosis
- Fever> 38^0c
- Grunting
- Hypothermia <38.8^0 C
- History of Convulsions
- Inability to feed or feeding difficulty
- Respiratory rate ≥60 breaths/min
- Severe chest wall indrawing

APPENDIX IV: QUESTIONNAIRE

PREVALENCE, ASSOCIATED FACTORS AND MANAGEMENT OF HYPERGLYCEMIA IN NEONATES ADMITTED WITH NEONATAL SEPSIS

Study number……

PART 1: SOCIO- DEMOGRAPHIC DATA

Neonate's Birth Details

1. Name of the baby (initials)…….……

2. Hospital IP number…….

3. Date of birth ……

4. Age of the neonate in days……

5. Sex Male ☐ Female ☐

6. Gestational age at birth in weeks……

7. Birth weight (g)……

8. Current weight (g)……

9. Mode of delivery: SVD☐ CS☐ Breech ☐

10. Place of delivery: Home☐ Health facility☐ Born before arrival to hospital☐

If health facility specify……

11. Duration of rupture of membranes in hours……

12. Cord care done using: chlorhexidine☐ surgical spirit☐ others☐. If others specify…

Maternal details

13. Age of the mother in years……

14. Marital status: Married☐ single☐ widowed☐

15. Level of formal education: Primary☐ Secondary☐ Post-Secondary☐ None☐

16. Employment: ☐Homemaker ☐Informal Formal☐

17. Average family income per month in KES:

< 5000☐ 5000-10000☐ 11000-20000☐ >20000☐

18. Insurance cover: None☐ NHIF☐ Others☐. If others please specify……

19. Parity……

20. Did she attend antenatal clinic Y☐ N☐

If yes, specify number of times she attended clinic……

21. HIV status during pregnancy: Positive☐ Negative☐ Unknown☐

22. History of gestational diabetes during pregnancy Y☐ N☐

If yes, any antenatal clinic record available to verify this: Y☐ N☐

23. Presence of hypertension during pregnancy Y☐ N☐

If yes, any antenatal clinic record available to verify this: Y☐ N☐

24. Presence of maternal fever during the last week prior to delivery Y☐ N☐

If yes, any antenatal clinic record available to verify this: Y☐ N☐

25. Did she attend post-natal clinic Y☐ N☐ N/A☐

If yes specify no of times……

26. Was she taught about how to express breastmilk? Y☐ N☐

If yes specify when she was first taught: antenatal period☐ postnatal period☐

27. Was she taught on exclusive breastfeeding Y☐ N☐

If yes, specify when she was first taught: antenatal period☐ postnatal period☐

28. Was she taught on positioning and attachment? Y☐ N☐

If yes, specify when she was first taught: antenatal period☐ postnatal period☐

29. Was breastfeeding or expressed breastmilk initiated after delivery Y☐ N☐

If yes, how soon after delivery? (in hours)……

30. Did the mother worry about having enough milk? Y☐ N☐

31. Did the mother have any breast conditions? Y☐ N☐

If yes specify……

32. Was the infant on any other feeds apart from breast milk prior to onset of illness? Y☐ N☐

If yes specify……

PART II: DISEASE VARIABLES

33. Duration of illness in days……

34. Was the child referred from another facility? Y☐ N☐

If yes, any referral notes indicating that dextrose was given? Y☐ N☐

35. Did the neonate receive any other medication (including herbal medication) before being brought to KNH? Y☐ N☐

If yes please specify……

36. History of diabetes in the first degree relatives of the subject Y☐ N☐

37. CLINICAL SIGNS AND SYMPTOMS: **Adapted from the KNH neonatal admission record.**

WEIGHT…… LENGTH----------TEMP(^{0}C) ……0_2 SATURATION……

HISTORY				EXAMINATION				
SYMPTOMS			DURATION IN DAYS	General	Jaundice		Y	N
				Breathing	Respiratory rate for 1 minute		……../Min	
Fever	Y	N			Central cyanosis		Y	N
Difficulty feeding	Y	N			Severe Lower chest wall in drawing		Y	N
Difficulty in breathing	Y	N			Grunting		Y	N
					Wheeze		Y	N
				Circulation	Pulse	Weak	Normal	….Min
					Cap.refill	< 3secs	>3secs	
Change in level of activity	Y	N			Pallor/Anaemia	0	+	+++
				Disability	Reduced movement/Floppy	Y	N	
Convulsions during this illness No in the last 12 hrs =	Y	N			Can suck or breastfeed	Y	N	
Diarrhoea	Y	N			Stiff neck	Y	N	
vomiting	Y	N			Bulging fontanelle	Y	N	
Vomits everything	Y	N			Irritable	Y	N	
Other complaints……				Abdomen	Distended	Y	N	

	umbilicus	clean	pus	pus plus red skin

Investigations done at admission

38**.** Blood Sugar level done at admission……mmol/l

39. Complete blood count done at admission: Y☐ N☐

If yes specify

a. White blood cell count: ……. $\times 10^9$ cells/l
b. Neutrophil count……$\times 10^9$ cells/l
c. Lymphocyte count……$\times 10^9$ cells/l
d. Haemoglobin level ……. g/dl
e. Platelet count ……. $\times 10^9$ cells/l

40. Renal function test done at admission Y☐ N☐

If yes specify

a. Urea (mmol/l)……
b. Creatinine (micromoles per litre)……
c. Sodium levels (mmol/l)……
d. Potassium levels (mmol/l)……

41. Blood culture at admission: Positive☐ Negative☐ No information☐

If positive specify organism grown……

42. CRP done at admission: Y☐ N☐

If yes specify in mg/dl……

Assessment of management (for those noted to be hyperglycemic)

43. Enteral feeds prescribed at admission: Y☐ N☐ No information☐

If yes, mode of feeding indicated: Nasogastric tube☐ Cup feeding☐

44. If nasogastric tube or cup feeding in number 43;

a) Type of feed prescribed:

Breastmilk☐ Formula☐ Both ☐ Others☐ (specify)……

b) Volume per feed indicated Y☐ N☐. If yes specify mls.……

c) Frequency in 24 hrs indicated Y☐ N☐.If yes specify ……

45. If no in number 43, were enteral feeds prescribed at any point during the first 24 hours after admission? Y☐ N☐

46. IV fluids prescribed at admission Y☐ N☐

47. If yes in number 46, was dextrose prescribed? Y☐ N☐.

If yes, type of fluid prescribed and volume (tick and fill as appropriate)

Type of fluid	Components of the fluid	Volume of each component per hour
Plain 5% dextrose	5% dextrose only	
Plain 10% dextrose	10% dextrose only	
10% Dextrose/Normal saline/potassium chloride(KCL)	10% dextrose	
	Normal saline	
	KCl	
5%Dextrose/Normal saline/KCL	5%Dextrose	
	Normal saline	
	KCL	
10%Dextrose/Ringer's lactate	10% dextrose	
	Ringers lactate	
5%Dextrose/Ringer's lactate	5% dextrose	
	Ringer's Lactate	

48. Insulin prescribed at admission Y☐ N☐.

If yes specify;

a) Dosage in international units (IU)……

a) Mode of administration: Infusion☐ intermittent☐.

If infusion specify rate per hour ……

If intermittent specify frequency……

49. Frequency of blood glucose monitoring during insulin therapy indicated: Y☐ N☐

If yes please specify……

50. If no in number 48, was insulin prescribed anytime during the first 24 hours after admission?

Yes☐ No☐.If yes

a. Dosage prescribed (in IU)……

b. Mode of administration: Infusion ☐ Intermittent☐

If infusion specify rate ……

If intermittent specify frequency

c. Frequency of blood glucose monitoring during insulin therapy indicated Y☐ N☐

If yes please specify……

d. Is it indicated whether dextrose infusion rate was changed before insulin was prescribed?

Yes☐ No☐

If yes specify new volume in mls/ hour……

e. Is it indicated whether the dextrose concentration changed before insulin was prescribed?

Yes☐ No☐

If yes specify new concentration …….

Outcome

51. Duration of hospital stay in days……

52. Outcome at discharge: Alive☐ Dead☐

APPENDIX V: BUDGET

	Remarks	Units	Unit Cost	Total (Ksh.)
Proposal Development	Printing drafts	1000 pages	5	5000
	Proposal copies	8 copies	1000	8000
Data Collection	Stationery pack (Pens & paper)	400	50	20000
	Research assistants training	1 day	1000	1000
	Research Assistants	12weeks	2000 X 2	48000
Data Entry	Data Clerk	1	7000	7000
Data Analysis	Statistician	1	35000	35000
Thesis Write up	Printing drafts	1000 pages	5	5000
	Printing Thesis	10 copies	1500	15000
Contingency Fund				10000
Total				**154,000**

APPENDIX VI: ETHICAL APPROVAL

UNIVERSITY OF NAIROBI
COLLEGE OF HEALTH SCIENCES
P O BOX 19676 Code 00202
Telegrams: varsity
Tel:(254 020) 2726300 Ext 44355

KNH-UON ERC
Email: uonknh_erc@uonbi.ac.ke
Website: http://www.erc.uonbi.ac.ke
Facebook: https://www.facebook.com/uonknherc
Twitter: @UONKNH_ERC https://twitter.com/UONKNH_ERC

KENYATTA NATIONAL HOSPITAL
P O BOX 20723 Code 00202
Tel: 725300-9
Fax: 725272
Telegrams: MEDSUP, Nairobi

Ref: KNH-ERC/A/399

8th November 2018

Dr. Emelda Manguro
Reg. No.H58/87616/16
Dept. of Paediatrics and Child Health
School of Medicine
University Health Services
University of Nairobi

Dear Dr. Manguro

RESEARCH PROPOSAL – PREVALENCE, ASSOCIATED FACTORS AND MANAGEMENT OF HYPERGLYCEMIA IN NEONATES ADMITTED WITH NEONATAL SEPSIS AT KENYATTA NATIONAL HOSPITAL (P603/08/ 2018)

This is to inform you that the KNH- UoN Ethics & Research Committee (KNH- UoN ERC) has reviewed and approved your above research proposal. The approval period is 8th November 2018 – 7th November 2019.

This approval is subject to compliance with the following requirements:

a) Only approved documents (informed consents, study instruments, advertising materials etc) will be used.
b) All changes (amendments, deviations, violations etc.) are submitted for review and approval by KNH-UoN ERC before implementation.
c) Death and life threatening problems and serious adverse events (SAEs) or unexpected adverse events whether related or unrelated to the study must be reported to the KNH-UoN ERC within 72 hours of notification.
d) Any changes, anticipated or otherwise that may increase the risks or affect 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.
e) Clearance for export of biological specimens must be obtained from KNH- UoN ERC for each batch of shipment.
f) 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*).
g) Submission of an *executive summary* report within 90 days upon completion of the study. This information will form part of the data base that will be consulted in future when processing related research studies so as to minimize chances of study duplication and/ or plagiarism.

For more details consult the KNH- UoN ERC website http://www.erc.uonbi.ac.ke

Yours sincerely,

PROF. M.L. CHINDIA
SECRETARY, KNH-UoN ERC

c.c. The Principa, College of Health Sciences, UoN
The Director, CS, KNH
The Chairperson, KNH-UoN ERC
The Assistant Director, Health information, KNH
The Dean, School of Medicine, UoN
The Chairperson, Dept. of Paediatrics and Child Health, UON
Supervisors: Prof. Grace Irimu, Prof. Rachel Musoke, Dr. Lawrence Owiro