SURVIVAL OF VERY LOW BIRTH WEIGHT NEONATES INITIATED ON EARLY VERSUS LATE ENTERAL FEEDING AT THE UNIVERSITY TEACHING HOSPITAL, LUSAKA

BY

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DECLARATION:

I, Dr. Bwendo Nduna, declare that this dissertation represents my own work and is being submitted for the Master's degree in paediatrics and child health at the University of Zambia, Lusaka. It has not been previously submitted for any degree or other qualifications at this or any other University.

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CERTIFICATION OF APPROVAL

I certify that this study, "A study to compare survival of very low birth weight neonates initiated on early versus late enteral feeding in the neonatal intensive care unit at The University Teaching Hospital, Lusaka" is the result of my own independent investigation.

Bwendo Nduna

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Examiner 1

Signature…… Date…….

Examiner 2

Signature…… Date…….

Examiner 3

Signature…….. Date…….

ABSTRACT

Background: In most neonatal intensive care units (NICUs), including the NICU at University Teaching Hospital (UTH), Lusaka, initiation of enteral feeds in very low birth weight (VLBW) neonates, is predominantly delayed for forty-eight to seventy-two hours, whilst they are commenced on intravenous fluids containing 10% dextrose. However, a proportion of stable VLBW neonates are fed. Delayed feeding presents challenges like low blood sugar in neonates, whereas early feeding can predispose them to necrotising enterocolitis (NEC). Thus a study to compare outcomes of early versus late feeding in this group was under taken.

Objective: To compare the mortality, occurrence of NEC and associated risk factors among VLBW neonates initiated on feeds early versus late.

Methods: This was a cohort study comparing outcomes between VLBW infants fed breast milk late or early during the period May to October 2014 in NICU at UTH. Patients were assigned to the feeding arms based on the clinical judgement of the attending doctor. Clinical parameters of those infants enrolled in the study were obtained from clinical notes and the patients were followed up to 28 days of life. The primary outcomes were death and occurrence of NEC. We compared risks of death or NEC in the late vs. early feeders.

Results: One hundred and forty eight new-borns were enrolled; 93 (63%) were girls and 55 (37%) were boys. The mean birth weight was 1.3kg. There was a total of 41 (30%) deaths recorded in this study, 35 (66%) occurred in the late feeders and 6 (6%) in the early feeders. There were 5 (3%) cases of NEC in the study, four were from the early feeders and one from the late feeders, three died (2= early feeders, 1=late feeder). Feeding status and birth weight were the only significant predictors of mortality.

Conclusion: Early feeding of very low birth weight neonates is associated with better survival than late feeding.

Recommendations: Early feeding of VLBW neonates in NICU, UTH will improve their survival. Randomised controlled trials need to be done to generate stronger evidence based conclusions.

Keywords: early feeding, timing, very low-birth-weight, necrotising enterocolitis, survival

DEDICATION

This work is dedicated to my dear loving and ever supportive husband, Dr Abidan Chilupe Chansa. My precious children, Chilupe and Jennifer Mweshi. My parents, Mr and Mrs C.F. Nduna and Mr and Mrs O. C. Chansa for always believing in me and holding my hand every step of the way. My ever supportive aunts and uncles who have watched me realise my dreams. My brothers, Chileshe, Mweshi, Mwewa, Lombe and Danny. My sisters Louisa, Chenge, Chitalu, Vera, Charity, Carol, Lydia and Musonda.

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LIST OF ABBREVIATIONS

ELBW – Extremely Low Birth Weight

LBW – Low Birth Weight

NEC – Necrotizing enterocolitis

NICU – Neonatal Intensive Care Unit

VLBW – Very Low Birth Weight

UTH – University Teaching Hospital

HM – Human Milk

WHO – World Health Organization

GI – Gastrointestinal

TPN – Total Parenteral Nutrition

EBM – Expressed Breast Milk

FBC – Full Blood Count

BWT- Birth Weight

RBS – Random Blood Sugar

SGA – Small for Gestational Age

CSPEN – Chinese Society of Parenteral and Enteral Nutrition

ZDHS – Zambia Demographic Health Survey

PROM – Premature Rupture Of Membranes

BWT – Birth Weight

OPERATIONAL DEFINITIONS

Neonate: Newborn in the first 28 days of life

Low Birth Weight Neonates: Babies born with birth weight between 1,500-2,499 grams

Very Low Birth Weight: Babies born with birth weight less than 1,500 grams

Small for Gestational Age: Babies who are smaller in size than normal for their gestational age

Necrotising Enterocolitis: Defined as any neonate who developed abdominal distension, vomiting, feeding intolerance in addition to clinical deterioration (lethargy)

Early feeding: VLBW neonates fed within 48 hours of birth

Late feeding: VLBW neonates fed after 48 hours of birth

Enteral feeding: Refers to feeding the VLBW neonates orally (breast/cup) or via naso-gastric tube

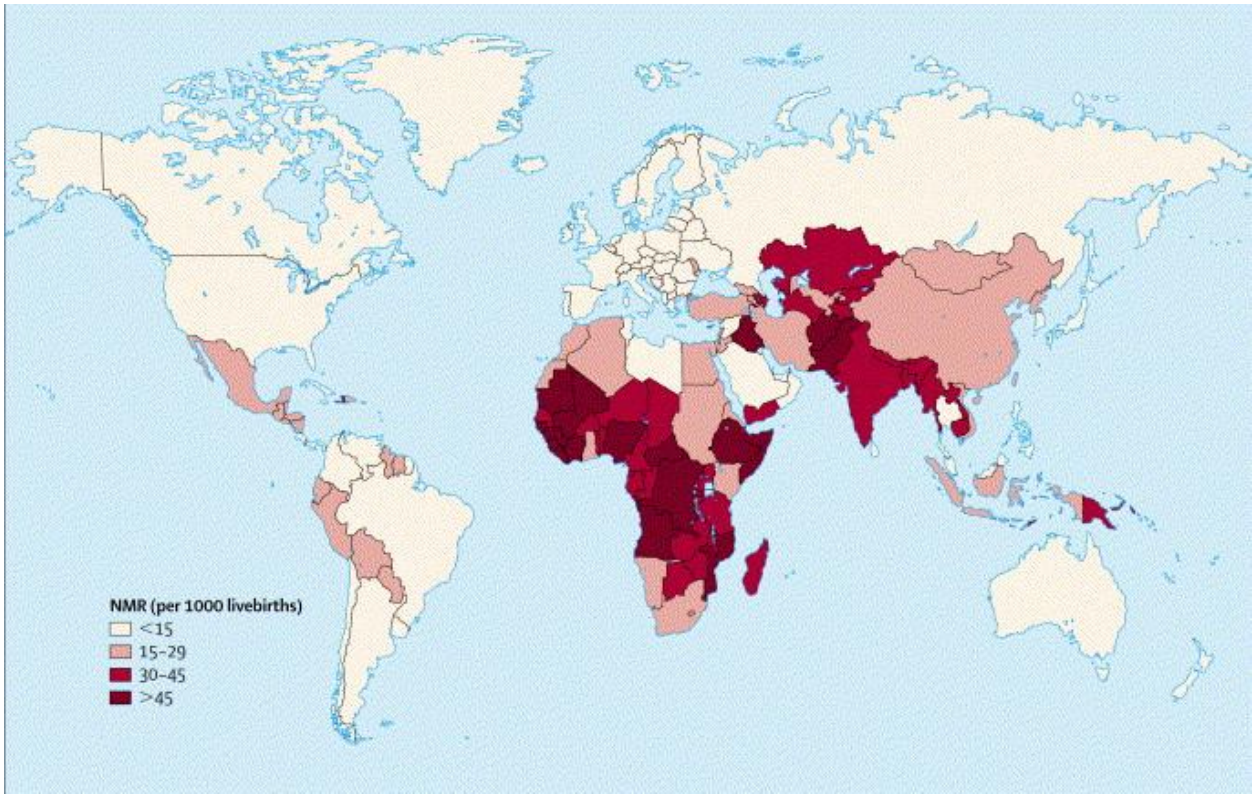
Preterm Infants: Babies born at less than 37 completed weeks of gestation

CHAPTER ONE

1.0 INTRODUCTION

According WHO factsheet of 2012, forty percent of under-five deaths occur in the neonatal period globally. Four million of the one hundred and thirty million children born each year die in the first 4 weeks of life (1). Ninety eight percent of neonatal deaths arise in less developed countries (2). Two-thirds of these neonatal deaths arise in Africa and South-east Asia. Most of the sub-saharan African countries have the highest rates of neonatal mortality (14 of 18 countries with neonatal mortality rates (NMRs) >45 per 1000). Countries with recent civil unrest, such as Sierra Leone and Liberia also have exceptionally high NMRs (1). Figure 1 below is a depiction of the variation of NMRs in different countries worldwide.

Figure 1. The variation of NMRs in different countries worldwide



(Adopted from Lancet 2005 by Lawn et al) (1).

The Zambia demographic health survey (ZDHS) of 2014 estimated NMR at 24 per 1,000 live births.

Globally, the main direct causes of neonatal death are estimated to be preterm birth (28%), severe infections (26%), and asphyxia (23%) (1). The causes of neonatal deaths are represented in a figure 2 below.

Figure 2. Causes of Neonatal Deaths

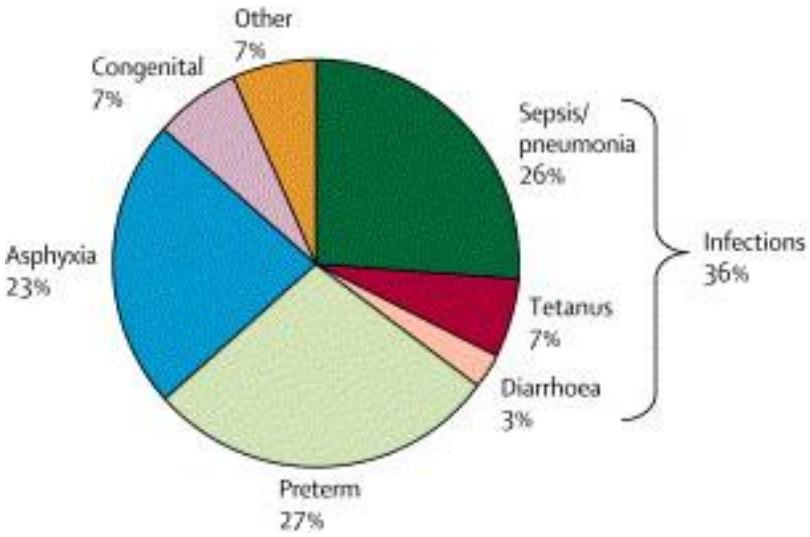


Figure 2 above is the estimated distribution of direct causes of 4 million neonatal deaths for the year 2000 based on vital registration data for 45 countries and modelled estimates for 147 countries. (Adopted from Lancet 2005 by Lawn et al) (1).

In humans, preterm birth is the birth of a baby of less than 37 weeks gestational age. Low birth weight (LBW) has been defined by the World Health Organization (WHO 2011) as weight at birth less than 2500g. LBW can be a consequence of preterm, or due to small size for gestational age (SGA, defined as weight for gestation less than 10th percentile), or both.

In relation to birth weight, most preterm babies are low birth weight (LBW), very low birth weight (VLBW) or extremely low birth weight (ELBW), as classified below:

Low Birth Weight: Babies born with birth weight between 1,500-2,499 grams.

Very Low Birth Weight: Babies born with birth weight less than 1,500 grams.

Extremely Low Birth Weight: Babies born with birth weight less than 1,000 grams.

The burden of LBW, VLBW and ELBW preterm neonates in Zambia is unknown. An unpublished review done in the Neonatal Intensive Care Unit (NICU) at the University Teaching Hospital (UTH) for admissions between December 2012 and May 2013 revealed that preterm neonates make up sixty percent of all admissions and are the second leading cause of death after asphyxia. ELBW and VLBW neonates make up for more than two thirds of these deaths with case fatality rates of eighty-eight and sixty-eight percent respectively.

Managing VLBW neonates present an array of challenges to the practicing paediatrician. These include timing of enteral feeding initiation, temperature maintenance, keeping the umbilical cord clean, skin care, and early detection and treatment of complications. The decision as to when to initiate enteral feeds is made difficult by the fact that the gastrointestinal (GI) tract is not fully developed, infection could pre-exist and the inability of most neonates to tolerate feeds.

In most neonatal intensive care units, UTH NICU included, initiation of enteral feeds is delayed for forty-eight to seventy-two hours while the neonate is commenced on intravenous fluids. A proportion of stable VLBW infants are however fed. This enables the paediatrician/neonatologist to make a thorough assessment of the neonate's ability to tolerate enteral feeds and thus initiate feeding at what is deemed to be the appropriate time.

This delay in initiation of feeds however is not without risks. These risks include neonates developing hypoglycaemia due to inadequate stores of glycogen in their immature liver. This is further compounded by incorrect and inappropriate administration of intravenous fluids. Intravenous-line related sepsis is a major probable risk as lines may frequently need to be changed due to viscosity of sugar containing fluids.

The ideal substance to feed neonates is colostrum/breast milk. Colostrum is the first stage of breast milk that occurs during pregnancy and lasts for a few days after the birth of the baby. It is high in protein, fat-soluble vitamins, minerals, and immunoglobulins (3). If enteral feeding is delayed, the neonate may lack the potential immune benefits that colostrum confers on them if the mother discards the first milk while they are not being fed. The benefits and risks need to be weighed against each other as far as the timing of initiation of enteral feeds is concerned. This study was designed to explore the merits and demerits of early versus delayed initiation of enteral feeding in VLBW neonates.

CHAPTER TWO

2.0 LITERATURE REVIEW

The development of the GI tract during intrauterine life for a human foetus is essential for survival in external life. The GI tract has digestive, absorptive, secretory, barrier, endocrine and immunological functions. The stomach at term has a volume of about 30 ml, the small intestine a length of 250-300 cm, the large intestine a length of 30-40 cm. The digestive and absorptive functions of the GI tract begin to appear around the 10^{th} week of gestation. The full expression of their activities begins between the 26^{th} week of gestation and term or within the first month of life. Although the digestive and absorptive capability of the GI tract is well prepared for external life after birth (even for premature babies), immature motility is the limiting system particularly for premature infants to cope with external feeding (4). The foetus is able to swallow amniotic fluid by as early as 11 to 12 weeks gestation. Mouthing can be observed at 15 weeks but the coordinated sucking movements are not usually present until about 28 weeks gestation. Single sucks can be recorded manometrically at 28 weeks and sucking bursts by 31 weeks gestation (5). A mature sucking pattern that can adequately express milk from the breast is not present until 32-34 weeks gestation (6).

The timing and constituents of the initial feedings in VLBW neonates remain a controversial issue among neonatologists (7). Starting full enteral feedings too early has been considered to predispose these infants to necrotizing enterocolitis (NEC) (8-11), a fulminant disease where portions of bowel undergo necrosis, which causes more than 400 neonatal deaths annually in the United States of America (12). NEC incidence is 3 to 10% in VLBW neonates (13-15) and is associated with increased mortality and morbidity, including growth and neurodevelopmental impairment (16-21). The pathophysiology of NEC is thought to involve immaturity of the immune, circulatory, and digestive systems (16) hypoxic-ischemic injury, enteral feeding, and pathologic bacterial colonization (22). Other studies however show that the primary risk factor for NEC is prematurity, because the incidence varies inversely with gestational age with 90% of cases occurring in pre-term infants and rarely in older infants and children (23, 24).

Apprehensions about NEC have prompted neonatologists to delay enteral feedings in favour of prolonged total parenteral nutrition (TPN) (25). This practice, however, is associated with complications such as cholestatic jaundice (26-28), metabolic bone disease (29) and sepsis (30) and may cause intestinal atrophy (31).

Enteral nutrition is necessary for intestinal growth and maintenance of normal GI function (32, 33). During the third trimester of pregnancy, the foetus swallows amniotic fluid, possibly providing significant luminal nutrition and trophic stimulation for the developing GI tract (34, 35). The very premature neonate is deprived of this luminal nutrition, which may contribute to subsequent poor feeding tolerance (25).

Human milk (HM) feeding has been associated with a lower incidence of NEC, infections and improved neurodevelopmental outcome as compared with formula feeding (36-40). A meta-analysis of four randomized clinical trials of donor HM versus formula suggests that 100% HM feeding is protective against NEC (39). Observational studies also have reported a lower incidence, among infants fed HM, of NEC (36) and NEC and sepsis combined (37).

Breast feeding has a significant effect on the growth, development, and function of the epithelium and immune and nervous systems of the GI tract and is an integral component of the infant's innate defense system. Properties in breast milk, such as cytokines, lactoferrin, glycoconjugates, oligosaccharides, white blood cells, and immunoglobulins, help protect the developing infant's GI tract from colonization by bacteria associated with NEC, as well as allergens (41).

Milk feeding is recommended to be initiated in stable infants >32 weeks gestation in the first 24 hours of life. However, the optimal timing of initiation of enteral feeding in infants <32 weeks gestation has been disputed. Practice differs considerably in developed and developing countries (42). A Cochrane review by Bombell S et al, which included three small trials in which a total of 115 VLBW weight infants participated with only a minority of participants being of ELBW or extreme preterm gestation, provided no evidence that delayed introduction of progressive enteral feeds affected the incidence of NEC (43). Therefore, there is evidence of benefit from initiation of early enteral feeding as early as clinically appropriate in stable low birth weight infants.

Another Cochrane systematic review, by Bombell S et al, summarized 10 trials of trophic feedings compared with no feedings in pre-term infants <33 weeks gestation, and one trial which compared trophic feedings with advanced feedings. They concluded that there is insufficient evidence to determine whether feeding VLBW infants small quantities of milk during the first week after birth (early trophic feeding) helps bowel development and improves subsequent feeding, growth and development (44). The same meta-analysis of nine

studies with 650 participants showed no significant difference in the incidence of NEC among infants given trophic feedings or no feedings. An update in 2013 by Morgan et al showed that there is no consensus on early or delayed feeding of VLBW infants and further trials would be required to determine how trophic feeding compared with enteral fasting affected this specific population (45).

Fasting is associated with reduced intestinal motility, intestinal mucosal atrophy, and a longer time to establish enteral nutrition. This is consistent with the idea that enteral nutrition is critical for normal intestinal function (46). However, the introduction of feeds in preterm infants is tempered by concerns about feeding intolerance, gastrooesophageal reflux, and/or necrotising enterocolitis.

Withholding enteral feeds however does not appear to prevent NEC (47), but small amounts of enteral feeds have been shown to stimulate surges in secretion of intestinal polypeptide hormone thought to be important in postnatal intestinal adaptation(48). Dunn et al prospectively examined the effects of early (day 3 of life) hypocaloric enteral nutrition (10–20 ml/kg/day) and reported less jaundice, osteopenia of prematurity and earlier establishment of full enteral feeds with the hypocaloric regimen (49).

Slage et al also examined the effects of early low volume enteral feed substrate (12 ml/kg/day) on intestinal function and noted improved feeding tolerance and earlier establishment of full enteral nutrition with the hypocaloric regimen (50). McLure and Newell have also reported increased intestinal motility in infants receiving minimal enteral nutrition (51). Since withholding feeds does not appear to prevent NEC, there is little reason not to begin early hypocaloric enteral feeds in these nutritionally vulnerable infants. Literature regarding infant feeding in sub Saharan Africa, especially areas where there is no TPN available is scanty.

CHAPTER THREE

3.0 STATEMENT OF THE PROBLEM

An unpublished review done in NICU, UTH between December 2012 and May 2013 revealed a case fatality of VLBW neonates of sixty eight percent. Clinically, the causes of death ranged from hypoglycaemia to complications of prematurity. There are no studies that have been done on optimal time to initiate enteral feeds in this specific group of neonates and whether that may impact on their mortality in the first twenty eight days of life.

The current standard of care for VLBW neonates which is in practice in the NICU, UTH protocols is to start 10% dextrose intravenous fluids for at least forty eight to seventy two hours postnatal without oral feeding of either expressed breast milk or formula. This is subject to clinical judgement as this is not an absolute contraindication to feeding early. Neonates are therefore prone to developing hypoglycaemia due to delayed feeding which is further compounded by the limited number of nursing staff needed to ensure the continuous intravenous infusion. In addition, there are no infusion pumps, as they are not adequate and most are not in good working condition.

With the growing number of premature deliveries according to the WHO fact sheet 2013, from increased multiple births, poor maternal health, greater use of assisted reproductive techniques and increased proportion of births among women over thirty four years of age, the problem worsens and mortality increases. Thus a study to determine survival rates in VLBW neonates who are fed early against those fed late needs to be undertaken to guide policy and improve practice.

3.1 STUDY JUSTIFICATION

This study is necessary to guide in the optimal time to feed VLBW neonates in order to help reduce their mortality rate and explore whether promoting early feeding can overcome the existing challenges of current practice by preventing deaths especially from hypoglycemia in the early days of life. Also as clinical equipoise still exists, this study may help to answer some questions on the optimal time to initiate feeds in these vulnerable neonates.

Given the current practices in the NICU, at the UTH, a viable alternative is to start oral feeds early consisting of mothers' milk and avoidance of formula due to the risk of developing NEC especially since we do not have facilities to offer parenteral nutrition. The benefits of

this, is promoting breast milk feeding and encouraging the participation of mothers in the care of the newborns, enhancing maternal-infant bonding.

In addition, it may also assist in developing recommendations and strengthening of the nutrition protocol in NICU at UTH.

3.2 RESEARCH QUESTION

Is early feeding compared to late feeding of breast milk associated with better survival among VLBW neonates admitted to the NICU at UTH?

3.3 NULL HYPOTHESIS

There is no difference in survival between VLBW neonates fed breast milk early and those fed late at the neonatal intensive care unit, UTH.

3.4 STUDY OBJECTIVES

3.4.1 General Objective

To compare survival between VLBW neonates initiated on feeds early versus late.

3.4.2 Specific Objectives

- To determine the mortality rate among VLBW neonates fed breast milk in the first 48 hours of life versus mortality of VLBW neonates fed breast milk after 48 hours of life.
- To compare occurrence of NEC between VLBW neonates fed breast milk in the first 48 hours of life versus VLBW neonates fed after 48 hours.
- To determine the risk factors associated with mortality and NEC in VLBW neonates fed breast milk in the first 48 hours of life versus VLBW neonates fed after 48 hours.

3.4.3 Study assumptions

There are many factors that lead to morbidity and mortality in VLBW newborns including maternal (maternal age, parity, co-morbidities), neonatal factors (sex, gestational age, weight, HIV exposure), health care provider factors (number of staff and their availability, level of training, attitudes, practices), and standards of neonatal care practices including feeding (oral, parenteral, early, late). This study focused on feeding, early or late.

CHAPTER FOUR

4.0 RESEARCH METHODS

4.1 Study Design

This was a cohort study; in which the case arm consisted of VLBW neonates who were fed breast milk "early" (< 48 hours of life), while the control arm were the VLBW neonates who were fed breast milk "late" (> 48 hours of life). Both arms were followed up to 28 days to observe the outcomes.

4.2 Study Site

The study was conducted at the Neonatal Intensive Care Unit at the University Teaching Hospital in Lusaka. UTH is the largest referral hospital in Zambia. NICU is situated 3 minutes away from the maternity block at UTH and is the main/primary referral site for all premature neonates in Lusaka. It has a bed capacity of 90. The staffing in NICU on average includes 8-10 doctors and 22 nurses with the nurse: patient ratio of 1:30 per shift.

4.3 Study Period

May – October 2015

4.4 Study Population

VLBW neonates weighing 1000-1500grams who were admitted to NICU, UTH who met the inclusion criteria were recruited.

4.5 Sampling

Convenience sampling of the VLBW neonates admitted to the NICU was done. All mothers with VLBW neonates were approached for possible recruitment into the study. Eligible babies whose mothers gave consent were assessed clinically and for the ability to feed by independent doctors in the NICU. Based on that assessment, they were assigned to early or late feeding arms. Both arms were monitored and followed up to 28 days.

4.6 Sample size

The sample size was calculated using EpiInfo version 6 making the following assumptions:

Mortality in the control arm = 60%

Expected mortality in the early feeders = 35%

At 95% confidence interval and power of 80%

Sample size required, assuming 10% drop out, total sample size = 140 (early=93, late=47)

4.6 Inclusion criteria

1. Neonates with birth weight 1000-1500g admitted to NICU at UTH.
2. Neonates whose parents consented.
3. Mother's able to breastfeed or provide expressed breast milk (EBM).

4.7 Exclusion criteria

1. Neonates who didn't cry at birth.
2. Neonates with congenital birth defects.
3. Neonates with co-morbidities such as respiratory distress syndrome (RDS), metabolic disorders and neonatal sepsis.
4. Babies of mothers who were not willing to breastfeed.

4.8 Procedures

1. All potentially eligible neonates were weighed using a Crown scale.
2. Mothers of eligible neonates were approached and the study was explained to them using the study information sheet.
3. Those mothers agreeing to participate in the study signed consent forms.
4. Once consent was obtained, an initial clinical assessment was done to obtain baseline clinical details (Birth weight, age, temperature, random blood sugar (RBS), haematocrit).
5. The attending doctors in NICU then evaluated the neonates using the NICU protocols on whether to feed or delay feeds. This decision was independent of the researcher.
6. Information such as weight, RBS, haematocrit, temperature and respiratory rate (RR) were collected on patient sheets, daily in the first 72 hours or earlier if indicated; then on day 5, 7, and weekly till discharge.
7. Patients were followed up until the first 28 days of life. If discharged before day 28, the participants were reviewed weekly till day 28.
8. In an event of a death, the cause of death was obtained from medical records.
9. On average four patients were recruited on a daily basis.

4.8 Data Entry/Management

1. Patients' information was anonymized with study identification numbers and filled out on a form.
2. The forms were then checked for any inconsistencies and completeness.
3. Double entry was used to enter the data on the Epidata software database.

4.9 Outcomes

4.9.1 Primary Outcome

Death rate within first 28 days of life between the two arms

4.9.2 Secondary outcome

Percentage of patients that developed NEC

4.10 Variables

4.10.1 Independent variables:

1) Gestational age
2) Weight
3) HIV status
4) RBS
5) Sex
6) Comorbidities during treatment
7) Anaemia
8) Mode of delivery
9) Parity

4.10.2 Dependent variables

1) Mortality in the first month of life
2) Proportion that develop NEC

4.11 Statistical Analysis

Data entered in the Epidata was transferred to SPSS for analysis;

i. **Descriptive statistics**: variables like gestational age, birth weights, presenting random blood sugar were expressed as means and/or medians and percentages, while sex, HIV status of mother were expressed as proportions or percentages.

ii. Analytical statistics

a. We calculated the relative risk and risk ratios of early versus late feeding and their Confidence Intervals.
b. Chi square test was done to measure associations between categorical/binary variables (gender, parity of mother, HIV status) against the outcomes (death rate and proportion of NEC).
c. Unpaired T-test was used to measure associations between continuous variables (Haematocrit, weight) against the outcomes (death rate and proportion of NEC)
d. Multi variate regression models were used to identify independent risk factors for mortality and NEC.

4.12 Ethical Considerations

Ethical approval was sought from the ERES CONVERGE IRB before the study was conducted. Permission to conduct the study at the UTH was sought from the Senior Medical Superintendent of the UTH.

The patients who were enrolled in the study were only those who met the inclusion criteria and had written informed consent. No study participant was coerced to enter the study by monetary, preferential clinical care or otherwise. Patients' safety was the priority in this study.

For those babies fed early, there was the danger of developing infections such as NEC which was however treated by stopping feeds and treating with antibiotics. For those babies fed late, there was a risk of developing low sugar if monitoring of blood sugar was not done regularly. In the event of developing low sugar babies were given 10% dextrose boluses at 5mls/kg and continued on an infusion of fluids till the sugar normalised.

Also, there was also the risk of babies developing infections from the frequent putting of cannulas and other minimal risks included the discomfort of a needle prick and bruising that may come with collecting blood samples as with every other invasive medical procedure. It was however ensured that all investigations and study procedures were performed by qualified personnel to enhance patient safety

Confidentiality was maintained at all levels of the study. Study participants were given an identification code rather than their name for identity purposes. Data obtained was kept under lock and key in the NICU and was only be accessible to the investigator and supervisor. However no need for the ethical regulation board arose for them to check the data.

CHAPTER FIVE

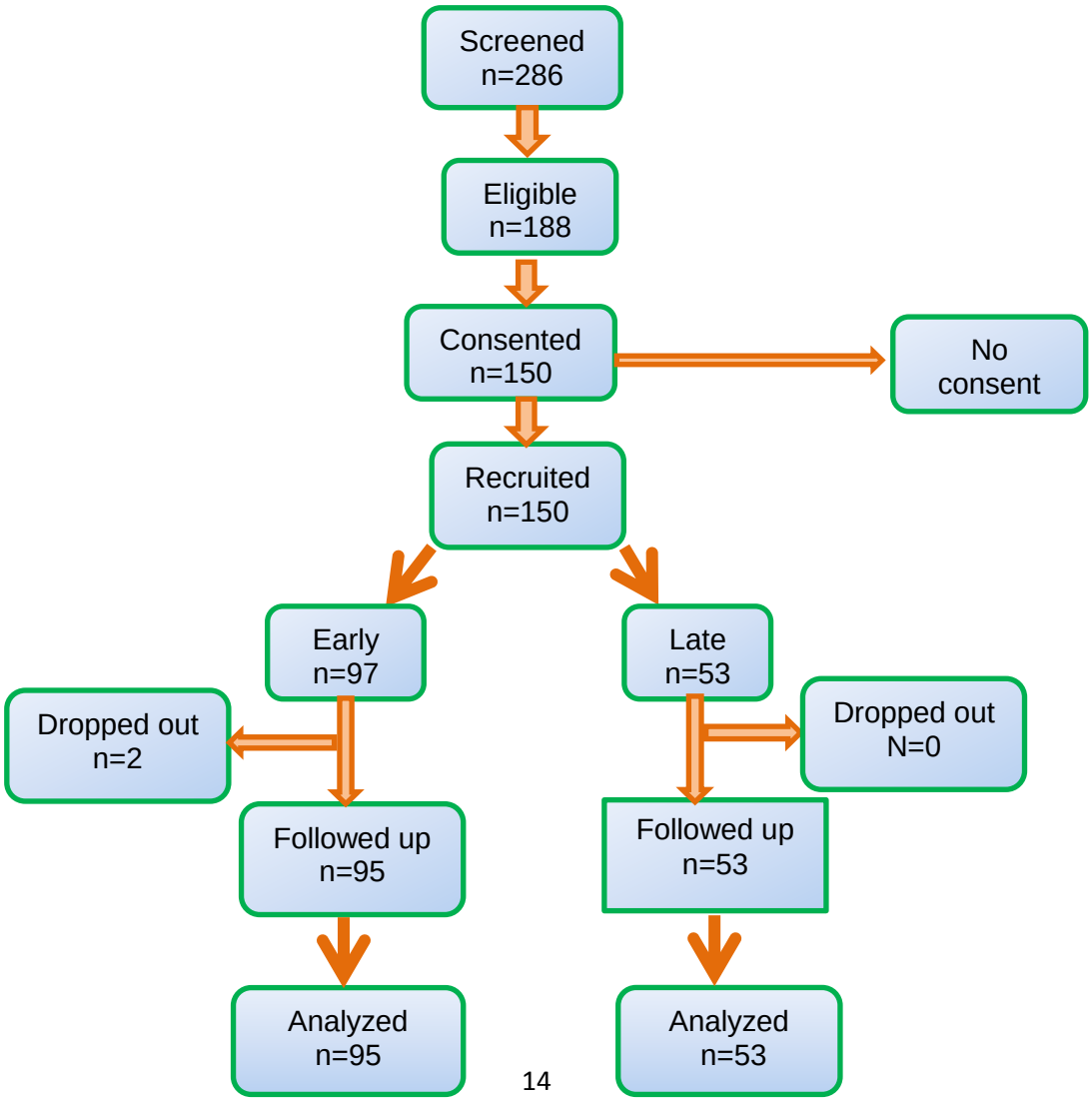
5.0 RESULTS

5.1 Recruitment Procedure

The number of neonates admitted to the NICU between May and October 2014 was 1687. A total of 286 neonates were screened for entry into the study. Of the 286 screened, the number of neonates that met the inclusion criteria was 188. The mothers to these neonates were approached for consent to join the study but only 150 consented and were recruited into the study.

Of the 150 children that were recruited into the study; ninety seven (66%) were fed early and fifty three (35%) neonates fed late. Two were excluded from analysis because of an incomplete data sheet and being lost to follow up giving a dropout rate of 1.3%. Therefore only 148 children were analysed. Figure 3 below is a flow chart of the recruitment process.

Figure 3. Flow Chart of Recruitment Process



5.2 Summary of participants

5.2.1 Neonate Characteristics

The total number of neonates enrolled into the study was 148. The average neonatal age on admission was 3.2 hours ± 3.05. In terms of sex distribution, there were more female neonates, (n=93, 62.8%) enrolled compared to males, (n=55, 37.2%). The median gestation period was 32 weeks (Range: 24 to 38 weeks). Eighty four (56.8%) of the children were of gestation period ≤ 30 weeks and 52 (35.2%) > 31 weeks. Fifty two (35.1%) of the children were HIV exposed. There were 119 (80.1%) children with AGPAR score at 5 minutes recorded. The mean AGPAR score was 8 with the lowest and highest scores being 4 and 9 respectively at 5 minutes. There were 103 (69.6%) children with AGPAR score ≥7 at 5 minutes. Table 1 below summarises the characteristics of the neonates enrolled into the study.

Table 1. Summary of Neonate characteristics

	Frequency (n/148)	**Percentage (%)**
Sex		
Male	55	37.2
Female	93	62.8
Gestational age		
≤30 weeks	84	56.8
>31weeks	52	35.2
HIV exposure		
Exposed	52	35.1
Un exposed	92	62.2
Unknown	4	2.7
Apgar scores		
4-6	16	10.8
≥7	103	69.6
Unknown	29	19.6
Presenting diagnosis from referral centre		
Asphyxia	3	2.1
Sepsis	2	1.4
Pre-term	143	96.5
Feeding status (Feed within 48hours)		
Yes (Early)	95	64.2
No (Late)	53	35.8

5.2.2 Maternal Characteristics

The mean age of the mothers to the neonates enrolled was 26 years (SD = 6.94). The youngest mother was aged 16 and the oldest 42 years old; fifty (33.8%) of the mothers were aged ≥30 years and 97 (65.5%) were aged < 30 years. Age was missing for 1 mother. Ninety eight (66.2%) of the mothers were married and fifty (33.8%) were unmarried. The median parity was 2 (range: 1 to 8). There were 22 (14.9%) mothers that delivered by caesarean section and 126 (85.1%) through spontaneous vaginal delivery. One hundred and thirteen (76.4%) of the mothers delivered from UTH while 35 (23.6%) delivered from other health centres or from home. Table 2 below summarises the maternal characteristics.

Table 2. Summary of Maternal Characteristics

	Frequency (n/148)	**Percent (%)**
Maternal Age		
≥30 years	50	33.8
<30 years	97	65.5
Parity		
1-2	75	50.6
≥3	73	49.3
Mode of Delivery		
SVD	126	85.1
C/S	22	14.9
Marital Status		
Single	50	33.8
Married	98	66.2
Place of Delivery		
UTH	113	76.4
Other facilities	35	23.6

Of the 148 mothers 5 (3.4%) had pre-eclampsia, 3 (2.0%) had premature rupture of membranes (PROM), 1 (0.7%) was hypertensive, 1 (0.7%) was eclamptic and none had diabetes mellitus. None of the mothers had sepsis and only 1 (0.7%) tested positive for

syphilis. Fifty two (35%) of the mothers were HIV positive. Table 3 shows co-morbid conditions in the mothers for the neonates enrolled.

Table 3. Mothers co-morbid conditions

Maternal illness	Yes [n(%)]	No [n(%)]	Treated	Not treated
Diabetes mellitus	-	148(100)	-	-
Hypertension	1(0.7)	147(99.3)	1	
Premature rupture of membranes (PROM)	3(2.0)	145(98.0)	2	1
Sepsis	-	148(100)	-	-
Pre-eclampsia	5(3.4)	142(96.6)	5	-
Eclampsia	1(0.7)	147(99.3)	1	-
HIV	52(35.1)	96(64.9)	38 (On HAART)	14 (Not on HAART)
Syphilis	1(0.7)	147(99.3)	1	-

5.3 Outcomes

There were a total of 41 (28%) deaths recorded in this study. Six (6.3%) out of the ninety five early feeders died compared to thirty five (66%) out of the fifty three of the late feeders. This is represented in a table below.

The Relative Risk (Risk ratio) was (6/95) / (35/53) = 0.09, CI = (0.04-0.20). In the study, 6% of neonates in the early feeding group died compared to 66% in the late feeding group. Early feeding reduced the risk of death by 0.91 or (1 – 0.09) or 91%. The absolute risk reduction (risk difference) was (35/50) – (6/93) = 0.69. The absolute risk of death in the early feeding group was 63.5% less than in the late feeding group.

Table 4. Relative Risk death of early vs. late feeders

		Death		Total	RR(CI)
		Alive [n(%)]	Death [n(%)]	[n(%)]	
Feeding Status	Early Feeder	89(94%)	6(6%)	95(100)	0.09 (0.04-0.20)
	Late feeder	18(34%)	35(66%)	53(100)	
Total		107(72%)	41(28%)	148(100)	

5.4 Association of study variables with Feeding Status

At 5% significance level, feeding status was significantly associated with mortality (P-value < 0.001) and gestation age (P-value = 0.001). Maternal age, marital status, parity, sex, and HIV status, were not statistically significantly associated with feeding status. APGAR score at 5 minutes was marginally associated with feeding status, P-value = 0.05. The Independent samples test for equality of means showed significance difference in weight at baseline (P-value < 0.01), but no statistical difference in RBS and neonate body temperature.

Table 5. Group statistics for T-test equality of means

	Feeding Status	N	Mean	Std. Deviation	Std. Error Mean	P-Value
Weight (kg)	Early Feeder	95	1.36	0.13	0.01	< 0.01
	Late Feeder	53	1.25	0.18	0.02	
RBS(mmols/L)	Early Feeder	95	3.23	1.64	0.16	0.29
	Late Feeder	53	2.93	1.62	0.22	
Temperature (ºC)	Early Feeder	95	35.01	1.53	0.15	0.96
	Late Feeder	52	35.00	1.37	0.19	

5.6 Bivariate analysis association

On bivariate analysis there was no significant difference between the two arms on the variables of maternal age, marital status, parity, mode of delivery and the neonates place of birth, sex, gestation age, HIV status, apgar score at 5 minutes and death (table 6). The gestational age was the only association shown to be significant between the two groups.

Table 6. Bivariate analysis comparing early vs. late feeders

Variable	Early Feeder		Late Feeder		P-value
	N	%	N	%	
Age					
< 30 years	58	59.8	39	40.20	0.14
30+ years	36	72.0	14	28.00	
Marital status					
Single	33	66.00	17	34.00	0.74
Married	62	63.30	36	36.70	
Parity					
1-2	47	63.50	27	36.50	0.78
3+	48	65.80	25	34.20	
Mode of delivery					
CS	12	54.50	10	45.50	0.31
SVD	83	65.90	43	34.10	
Place of birth					
Other	19	54.30	16	45.70	0.16
UTH	76	67.30	37	32.70	
Sex					
Female	60	64.50	33	35.50	0.91
Male	35	63.60	20	36.40	
Gestation (Weeks)					
≤ 30	31	49.20	32	50.80	<0.01
>31	63	75.00	21	25.00	
HIV status					
Exposed	33	63.50	19	36.50	0.94
Unexposed	59	64.10	33	35.90	
APGAR Score at 5 minutes					
4-6	7	43.80	9	56.30	0.05
≥7	71	68.90	32	31.10	
Death					
Yes	6	14.60	35	85.40	<0.01
No	89	83.20	18	16.80	

5.5 Logistic regression analysis

The relationship between study variables and death was examined using logistic regression. Selection for logistic regression model was considered at level P < 0.20 or known clinical significance. The study variables baseline weight, maternal age, place of birth, gestation age, and 5 minutes APGAR score were entered into a logistic regression model and the backward selection method was used to obtain the final logistic regression model. The backward selection method removes terms one at a time beginning with the largest p-value and continuing until all remaining effects are significant at a specified level or removing more terms results in poorer fit. Thus, the final model had feeding status and birth weight as the only significant factors in predicting neonatal death. Adjusting for birth weight Early Feeders had 98% reduced odds for death compared to Late Feeders (OR = 0.02, CI = 0.006 – 0.09, P-value <0.001). Adjusting for feeding status for a 1Kg increase in birth weight, the odds for death reduced by 97% (OR = 0.03, CI = 0.001 – 0.97, P-value = 0.048).

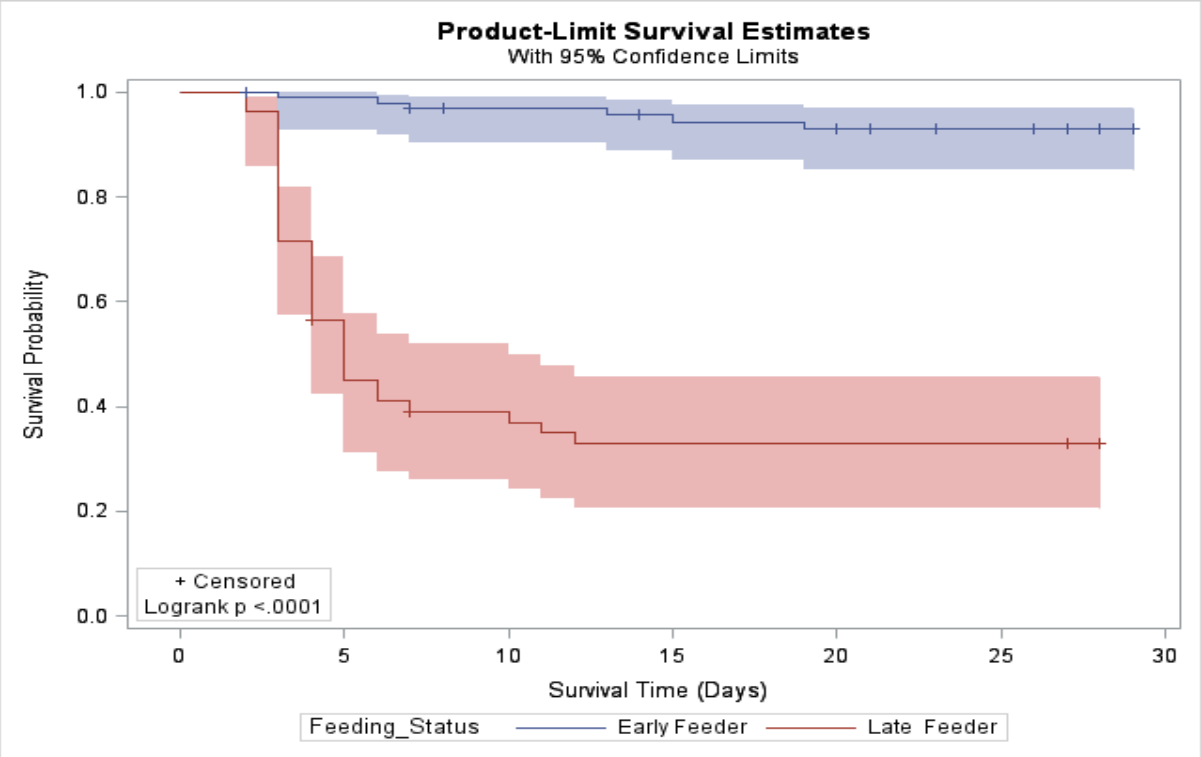
Table 7. Logistic regression analysis of the primary outcome (death) against feeding status and birth weight

Variable	**Unadjusted Odds Ratio (95% CI)**	**Adjusted Odds Ratio (95% CI)**	**p-value**
Feeding Status			
Late feeder	1	1	
Early feeder	0.03 (0.01 – 0.08)	0.02 (0.006 – 0.09)	< 0.001
Birth weight	0.02 (0.002 – 0.15)	0.03 (0.001 – 0.97)	0.048

5.6 Survival analysis

The figure below shows the Kaplan-Meier curves for survival probability of the neonates calculated from birth and stratified by feeding status. About 35% of late feeders survived at least the first 28 days of life and over 90% of early feeders survived at least the first 28 days of life. Survival between Early and Late feeders was significantly different, Logrank P <0.0001.

Figure 4. Survival Probability of Neonates by feeding status



NEC

There was a total of 5 (3.4%) cases of NEC. The cross-tabulation of NEC and death outcome for cases without missing NEC information is provided below.

Table 8. Cross tabulation of the NEC cases

	Early [n(%)]	**Late [n(%)]**
NEC	4 (4.2%)	1 (1.8%)
No NEC	91 (95.8%)	52 (98.2%)
Total	95 (100)	53 (100)

Out of the five cases of NEC, 1 was from the late feeders and 4 from the early feeders. Three of the five neonates with NEC died. One was from the late feeders and two were from the early feeders.

CHAPTER SIX

6.0 DISCUSSION

The study showed better survival of VLBW neonates fed within 48 hours of birth (early feeding) compared to those fed after 48 hours. This was particularly noted in those that had higher birth weights. This observation is similar to the findings of a systematic review done by Dutta S. et al (52) on a similar patient population which showed that early trophic feeding (<24hrs) of VLBW infants had improved outcomes. The Chinese Society of Parenteral and Enteral Nutrition (CSPEN) guidelines for nutrition support in neonates (53) also advocates that feeding should be initiated within 12 hours of birth for those with a birth weight of >1000grams. In our study all patients had a birth weight above 1000g and thus we agree with the CSPEN guidelines that there are better outcomes in those VLBW neonates fed early. Our mean time of feeding in the early feeders was 20 hours. Data from the review done by Barone G. et al (54) supports that VLBW infants fed early have better outcomes. In their review they included SGA (small for gestational age) infants and found that they had better outcomes as well. In our study the mean gestational age was 32 weeks and probably had SGA infants included as the inclusion criteria for our study was weight based.

The other literature are in support of early feeding due to be improved outcomes and being advantageous to the VLBW neonates include a review done by Baron G. et al (54), Slage et al (50), and McLure and Newell (51). We attributed the improved survival of early feeding in our study probably because the early feeders firstly, had a higher mean birth weight of 1.37kg as compared to 1.25kg of the late feeders. Secondly, the majority of late feeders had a lower gestational age (<30 weeks) and poorer apgar scores (4-6) at 5 minutes compared to the early feeders whose majority gestational age was >30 weeks and most had better improved apgar scores (>7) at 5 minutes. In addition the late feeders had a higher probability of sepsis and general poor wellbeing from admission as they were probably deemed as being ''unstable'' to feed meaning they'd be expected to have a poor outcome despite their feeding status.

Our study showed a low incidence of NEC between the two feeding arms. NEC was diagnosed clinically in our study. The parameters used were abdominal distension, absent bowel sounds, bilous vomiting or any feeding intolerance, in addition to the deterioration in general clinical condition. There were 5 (3.4%) cases of NEC recorded; 4 of these were in the early feeders and 1 was in the late feeders. As mentioned earlier, three of the five

neonates with NEC died, 2 from the early feeders and 1 from the late feeders. Due to the few numbers, it was not possible to generate conclusions as to why the early feeders appeared to record a higher number of cases of NEC. This was not as comparable to what Lucas and TJ Cole (36) found in a prospective multicentre study on 926 preterm infants who were assigned to their early feeding diet (which was either expressed breast milk or formula feeds). In their study, NEC developed in 51 (5.5%) of the 926 neonates followed up and 13 (26%) died. The incidence of NEC was much higher in those neonates that received formula feeds. In our study all the neonates were fed breast milk. We felt that the low incidence of NEC in our study may have been explained by our small sample size. Some literature indicates that the incidence of NEC is 3-10% (13-15), probably UTH, NICU, Lusaka is in low risk zones, probably due to the fact that a lot of Zambian women opt to breastfeed other than use formula feeds. Another factor to consider is that the low incidence of NEC could be explained because some cases may have been un-diagnosed or missed by the attending doctors in NICU. Also, the majority of the participants may probably have been small for gestational age, rendering them having slightly more mature gut function than the 'true preterm'' neonate even though SGA infants are prone to development of NEC either way (54). Due to the few cases of NEC recorded, we were unable to generate any risk factors as this was statistically insignificant.

In our study, morbidity in the mothers did not impact on outcomes in these neonates. There was only one mother who was hypertensive. Three (2.0%) of the mothers had PROM and this did not significantly impact on neonatal outcomes due probably to the small number of them enrolled. We had a total of 52 (35%) neonates who were exposed to HIV. Thirty eight (73%) of the mothers with HIV disease were on highly active anti-retroviral therapy (HAART). Of the neonates that were exposed to HIV, 33 (64%) were assigned to the early feeding arm while 19 (36%) were late feeders. There was no significant difference in survival in these two groups.

Gestational age of the neonates impacted on their mortality in our study. We observed that with increased gestational age, the odds of death decreased. The majority (75%) of the early feeders were > 31 week's gestation as opposed to 25% of the late feeders. This probably explained why the early feeders had better survival in comparison to the late feeders as the majority of them were born ≤ 30 weeks, thereby having an increased risk of death. The gestational age did not appear to have any effect on the incidence of NEC (which was low as

mentioned earlier) though it has been known in literature that the incidence of NEC is inversely related to an infant's birth gestation (55-58).

Low Apgar score (4-6) was associated with poorer neonatal outcomes compared to neonates with Apgar score ≥ 7 though this was not statistically significant. One hundred and three (86%) of the neonates enrolled with documented 5 minute Apgar scores to our study had scores ≥ 7. A study by Lee H et al (59) showed that low apgar scores were associated with increased mortality in premature neonates. They had analysed a total of 690, 300 neonates' records between gestational age 24-36 weeks and found the median 5 minute Apgar scores to be 8 and 9 in the 27-29 week gestation and 30-36 week gestation period respectively which was similar to our study which had a median 5 minute apgar score of 9. A retrospective analysis by Cassy B et al (60) concluded that the 5-minute apgar score has remained a valid predictor of neonatal mortality in term neonates. Hegyi T et al (61) also noted that a low apgar score was limited in predicting morbidity and mortality in term neonates. However, there is still no consistent data on the significance of the Apgar score in pre-term infants (62). Catlin E et al (63) observed that healthy preterm infants with no evidence of asphyxia could receive a low score only because of immaturity. This was not as evident in our study as the neonates mean 5 minute Apgar score was 8.

The results show that the birth weight of the neonates had significant difference between the two feeding arms (Early feeders mean birth weight (BWT): 1.37kg and late feeders mean BWT: 1.25kg) as already mentioned earlier which could have influenced survival. However, there was no statistical difference in presenting RBS and neonate body temperature on admission between the two feeding arms though the mean RBS in the early feeders was slightly higher (3.2 mmols/L) than those in the late feeders (2.9 mmols/L) rendering most of the late feeders as being hypoglycaemic from admission which could possibly help explain the poor survival in that group. There are still controversies (64) regarding the definition of neonatal hypoglycaemia though the protocols at NICU, UTH define hypoglycaemia as an RBS < 2.8mmol/L.

Interestingly the study showed that the neonatal characteristics were not as consistent as those reported in literature in regards to gender. The male gender is usually associated with a significantly higher risk of preterm birth (65, 66) which was not reflective in this study. We had more female neonates making up 62% of the study population as compared to 37% being male.

CHAPTER SEVEN

7.0 CONCLUSION

The study concluded that early feeding was associated with better outcomes in those very low birth weight neonates fed early (within 48 hours) at NICU in UTH. It was also evident that the very low birth weight neonates with lower birth weights had poorer outcomes. The incidence of necrotising enterocolitis in this study was low and thus did not impact on the outcomes of the very low birth weight neonates.

7.1 Study Limitations

- The inclusion of neonates was based on their weight resulting in possible inclusion of SGA neonates. SGA neonates are actually more mature than the ”true preterm’’ neonates except for their retarded growth in utero so they may have more mature GI function thereby affecting the outcomes since they would have better feeding tolerances than the preterm neonates.
- The diagnosis of NEC was clinical and not accompanied by radiological studies. This could have affected our actual detection of NEC cases as we may have had some undiagnosed cases especially in the neonates who died from sepsis. As much as NEC is predominantly a clinical diagnosis, radiological confirmation is also required.
- There could have been an element of bias in patient decision to start feeds by the independent doctors in NICU resulting in better outcomes to the early feeders as they may not have been predisposed to sepsis initially. Usually the decision to feed the neonates in NICU at UTH is based on a thorough clinical assessment and so any neonate who is deemed ‘’unstable’’ probably has early sepsis which is already a big contributor to neonatal mortality and morbidity whether or not the child is fed early or late.
- The sample size was too small to generate stronger conclusion

7.2 Recommendations

- A randomized controlled trial needs to be done in order to generate stronger conclusions.
- Early feeding of VLBW neonates may appear to improve survival in NICU**.**

CHAPTER EIGHT

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CHAPTER NINE

9.0 APPENDICES

9.1 Patient Information

Thank you for your interest in this study.

My name is Dr Nduna Bwendo of Lusaka Woodlands extension plot number 85356. I am studying to be a doctor for children at The University Teaching Hospital under the University of Zambia.

You are invited to take part in this study.

STUDY TITLE: A study to compare survival of very low birth weight neonates initiated on early versus late enteral feeding in the neonatal intensive care unit at the University Teaching Hospital in Lusaka

This study is trying to find ways that we can improve treatment of many premature babies that are admitted to our new born baby ward at the University Teaching Hospital in Lusaka by feeding them early as compared to feeding them late. Also we want to find out whether feeding early can improve survival of these premature babies.

If you accept to take part in this study, you will sign a form. The babies will then be checked by doctors working in the new born baby ward who will decide whether they will be fed with breast milk within 2 days or later after 2 days. The baby will then have blood taken for a full blood count (FBC), haematocrit, random blood sugar and HIV test.

Once your baby joins this study, your information will be private and your personal information will be given a private number.

Who is eligible to be recruited in the study?

Newly born babies who are less than 2 days old whose parents have agreed to take part in the study and those who are ready to breastfeed.

What are the benefits of you joining this study?

The benefits of joining this study are that we will help buy medication and pay for tests that may not be done at UTH. Also we will help to improve the way we take care of the babies in newly born baby ward which will help the whole general public in the long run.

Are there any risks involved in your participation in this study?

For those babies fed early, there is the danger of some infections e.g of the intestines. This condition however is treated by stopping feeds and treating with antibiotics.

For those babies fed late, there is a risk of developing low sugar if monitoring of blood sugar is not done regularly. There is also the risk of babies developing infections from the frequent putting of cannulas.

Other minimal risks involved include the discomfort of a needle prick and bruising that may come with collecting blood samples as with every other invasive medical procedure.

What will happen to you in case you decide to leave the study?

You are free to decide not to join in the study or withdraw your baby from the study at any point. Your baby's care will not be affected in any way neither will you be treated badly by any member of staff.

We will not give you any money for taking part in the study as this is voluntary.

If your baby is discharged before the study ends (within 28 days), transport money refund will be given to you should any reviews be needed.

Who do you contact in case of any questions or clarifications regarding the study?

You can contact me, Dr Nduna Bwendo, on mobile phone number +260 966183841 or e mail address: bwendon@yahoo.com

My supervisor, Dr Suwilanji Sinyangwe on mobile number +260 97788791 or e mail address: s_sinyangwe@yahoo.co.uk

My co-supervisor, Dr Chishala Chabala, on mobile number +260 0977849537 or e mail address: cchabala@yahoo.com

ERES CONVERGE IRB Chairperson, on mobile +260 955155633, e mail: eresconverge@yahoo.co.uk

9.2 Chidziwitsio cha odwala

Zikomo pa chidwi canu muphunziro iyi

.

Dzina langa ndine Dr Nduna Bwendo waku Lusaka woodlands extension plot number 85356. Niphunzila kukhala dotolo wa ana pa university teaching hospital pa university of Zambia

Ndinu oyitanidwa kutengako mbali muphunziro iyi.

MUTU WA PHUNZIRO: **Phunziro yoyelekeza kupulumuka kwa makanda Obadwa ndi Skelo yochepekela kwambiri ndi wochedwa kuyamba kudyesewa ndi chubu yodyeselako mu intensive care yamakanda, pa university teaching hospital mu Lusaka.**

Phunziro iyi iyesesa kupezan jira zoonjezer kuchita bwino pa kasamalidwe ndi kasungidwe ka ana ambiri osakhuma (osakosa) omwe asungidwa ku ward ya ana obadwa mwatsopano pa university teaching hospital mu Lusaka powadyesa mwamusanga kuyelekeza ndi kuwadyesa mochedwa. Tifunanso kupeza ngati kudyesa msanga kungaonjezere pakupulumuka kwa ana osakhuma.

Ngati muvomera kutengako mbali muphunziro iyi, muzafwatika pa pepala. Ndipo ana azaonewa ndi madotolo osewenza mu ward ya ana obadwa mwatsopano omwe azalamula kapena azapatsiwa mukaka wakubele(ziba) mwa masiku awiri olo patapita masiku awiri. Ndipo mwana azatengedwa magazi kukapima full blood count (FBC), haematocrit, sugar ndi HIV.

Pambuyo pamwana wanu kulowa muphunziro iyi, chidziwitso canu chizakhala chobisika ndipo chizapatsidwa nambala yobisika.

Ndani akwaniritsa muyeso wosankhidwa kutengako mbali muphunziro?

Ana obadwa mwatsopano ochepekera masiku awiri omwe makolo awo avomera kutengako mbali muphunziro ndipo azimai awo ndiwokonzeka kuyamwisa(kunyonsha).

Kodi ndimwathandizo lotani inu potengako mbali muphunziro iyi?

Mathandizo akutengako mbali muphunziro iyi ndiakuti tizakuthandizani kugula mankhwala ndi kulipila zopina zomwe sizichitidwa pa UTH. Ndiponso tizakuthandizani kuonjezera zakusamalira ana mu ward ya ana obadwa mwatsopano comwe cizathandiza anthu ambili mwanthawi.

Kodi kulizoyopsya zilizonse kwa inu pakutengako mbali rnuphunziro iyi?

Kwa ana odyesewa mwamusanga Kulichiopyezo cha matendam wachitsanzo ya kumatumbo. Iyi nthenda ichiritsiwa ndikuleka kudyesa ndi kupasa mankhwala

Kwa ana odyesewa mochedwa kulichiopyezo chokhala ndi sugar yayingono mumagazi ngati sugar siipimidwa pafupi pafupi. Kulinso chiopyezo ana kuyamba kudwala kuchokera ku kuikidwa kwapafupi pafupi kwa tumanyeleti tochedwa canula.

Zina zoopyeza zapangono ndi kusamveka bwino kwa kutwingiwa nanyeleti ndikukwalaulidwa komwe kubwela ndi kutenga magazi yokapimiwa monga mwa mndondomeko wazina zones zachipatala.

Ndichiani chizachitika kwa inu ngati mwaganiza kuleka phunziro?

Ndinu omasuka kusatengako mbali kapena kuleketsa mwana wanu muphunziro panthawi Iliyonse. Chisamaliro chamwana wanu sichizakhuzidwa njira iliyonse.

Kapena kuti simuzasungidwa bwino ndi wanchito aliyense.

Sitizakupasani ndalama iliyonse potengako mbali muphunziro iyi popeza ndi mwaufulu.

Ngati mwana wanu wachoka muchipatala nthawi yaphunziro ikalibe kusila (mwa masiku minyezi iwiri, chisanu ndi zitatu (28) muzapasidwa ndalama yokwelela galimoto ngati kuzafunika kumuona mwana.

Ndani okamba naye ngati muli ndifunso iliyonse kapena chomwe mufuna kumasulilidwa kukhuza phunziro?

Mungatumire ine Dr Nduna Bwendo pa +260 966 183841 kapena pakeyala iyi bwendon@yahoo.com.

Dr Suwilanji Sinyangwe pa +260 97788791 kapena pakeyala iyi s_sinvangwe@yahoo.co.uk

Dr Chishala Chabala pa +260 97'78 49537 kapena pakeyala iyi cchabala@yahoo.com

ERIS converge IRB Chairperson pa +260 955 155633 kapena pakeyala iyi eresconverge@vahoo.co.uk

9.3 Consent Form

I, ……, mother/father/guardian to the patient do accept to take part in this study with the title 'A study to compare survival of very low birth weight neonates initiated on early versus late enteral feeding in the neonatal intensive care unit at the University Teaching Hospital in Lusaka.' I have been availed the study information sheet and I understand what the study is all about. I understand the benefits and risks involved in my baby's participation in this study. I was given sufficient time to read/explained to about the study information and I asked questions and the answers given were satisfactory.

I also know that I can withdraw my baby's participation in the study without my clinical care being compromised.

I do know that my particulars in the study will be anonymous.

I do hereby accept for my baby to be enrolled in the study.

Name and Signature/thumb print of parent/guardian Date

…….

Name of person obtaining consent Date

……

Name and signature of Witness Date

…….

9.4 Data Collection Tool

Enrolment details

Date:

Time:

Index number:

UTH file number:

Interviewer initials:

Mother's details

Name:

Age:

Study ID:

Marital status:

Parity:

Mode of delivery:

Place of delivery:

Maternal co-morbid conditions

Maternal illness	Yes	No	Treated	Not treated
Diabetes mellitus				
Hypertension				
Premature rupture of membranes				
Sepsis				
Pre eclampsia				
Eclampsia				
HIV				
Syphilis				

Neonate details

Index number:

Date of birth:

Time of birth:

Age on admission:

Sex:

Gestation:

HIV exposed? Yes No

	At birth	At 1 minute	At 5 minutes
APGAR score			

Presenting diagnosis	Yes	No
Asphyxia		
Sepsis		
Preterm		

Feeding Assessment

Feed within 48 hours? Yes No

Not fed within 48 hours? Yes No

Age at feeding onset:

Clinical assessment

Assessment Date:	Day 1	Day 2	Day 3	Day 5	Day 7	Day 14	Day 21	Day 28
Weight								
Respiratory rate								
RBS								
Temperature								
Hematocrit								

OUTCOMES

	Yes	No
NEC		
Death		
Discharged alive		

1. If dead, age at death:
   Date of death:
   Time of death:
   Cause of death:

2. If developed NEC, age at diagnosis of NEC:
   Date of diagnosis:
   Time of diagnosis: