EFFECTS OF EARLY FEEDS WITH MOTHERS' MILK AMONG NEONATES WITH VERY LOW BIRTH WEIGHT AND HYPOXIC ISCHAEMIC ENCEPHALOPATHY ADMITTED AT REGIONAL REFFERRAL HOSPITALS IN DAR ES SALAAM, TANZANIA

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By

Regina Hyera

A Dissertation Submitted in (Partial) Fulfillment of the requirements for the Degree of Masters of Medicine (Pediatrics and Child Health) of

Muhimbili University of Health and Allied Sciences
October, 2019

CERTIFICATION

The undersigned certify that they have read and hereby recommend for acceptance by Muhimbili University of Health and Allied Sciences a dissertation entitled: **''Effects of early feeds with mothers' milk among neonates with very low birth weight and hypoxic ischaemic encephalopathy admitted at regional referral hospitals in Dar es Salaam, Tanzania'',** in (partial) fulfillment of the requirements for the degree of Master of Medicine (Paediatrics and Child Health) of the Muhimbili University of Health and Allied Sciences**.**

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DECLARATION AND COPYRIGHT

I, **Dr. Regina Octavian Hyera**, I declare that this **dissertation** is my own original work and that it has not been presented and will not be presented to any other University for a similar or any other degree award.

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First and foremost, I thank God who has kept me healthy and strong throughout my study. Glory be to God.

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DEDICATION

I dedicate this dissertation to my daughters **Gracelyne G. Mdede and Pauline G. Mdede** who were asking and waiting day and night for her mom to come back from studies.

ABSTRACT

Background: Early enteral feeding is usually delayed in neonates with very low birth weight and hypoxic ischaemic encephalopathy due to unstable haemodynamics and the risk of necrotizing enterocolitis. This prevents these neonates from receiving beneficial effects of colostrum hence predisposing them to an increased risk of infections, poor growth and development, and even mortality. Minimal enteral feeding and oral mucosa colostrum administration are feeding options available that can be used safely among unstable neonates, but these methods are not utilized in most of neonatal intensive care units.

Aim: To determine effects of early feeding using mother's milk on the early neonatal outcomes compared to nil orally standard feeding practices amongst neonates with very low birth weight and hypoxic ischaemic encephalopathy admitted at regional referral hospitals in Dar es Salaam.

Methodology: A quasi-experimental study was used to evaluate the effects of early infant feeding amongst neonates with very low birth weight and hypoxic ischaemic encephalopathy in Dar es Salaam between October 2018 and April 2019. The intervention consisted of early fed neonates either by minimal enteral nutrition or oral mucosal colostrum within 24 hours and controls received routine care - nil per oral until when considered haemodynamically stable. The primary outcome was the occurrence of necrotizing enterocolitis while the secondary outcomes were neonatal mortality, time to regain birth weight and duration of hospital stay.

Data analysis was done by using SPSS version 20. Categorical variables including occurrence of necrotizing enterocolitis and mortality were presented as proportion. Continuous variables were summarized by using mean (standard deviation) or median (inter quartile range) depending on whether they were normally distributed or not, respectively. Chi-square test (or when appropriate Fishers exact test) was used to compare statistical significance in outcomes that were measured as proportions. Odds ratio (OR) was used to determine the association between feeding and dependent variables. The results were considered of statistical significance when P-value was$\leq$0.05.

Results: A total of 292 neonates were enrolled in this study, 55.8% (163) were controls and 44.2% (129) were in the intervention group. Study participants comprised of 44.5% (130) neonates with Very low birth weight (VLBW) and 55.5% (162) with hypoxic ischaemic encephalopathy (HIE). The mean age of initiating feeding was 45.34 ± 21.58SD hours in the control group and 8.43 ± 3.02SD hours in the intervention group (p-value = 0.000). Overall, 1.4% (4cases) of neonates enrolled in the study had necrotizing enterocolitis, 1.8% (3cases) from the control group and 0.8 %(1case) from the intervention group (P=0.4, 95%CI: 0.25-23.3). The overall mortality was 40.8% (119), with no significant difference in mortality between the control group and intervention group, 41.7% vs.39.5 % respectively (p= 0.071, 95%CI: 0.57-1.46). The mean duration of regaining birth weight was 11.26 ± 4.34SD days in control group and 8.25 ± 2.96SD days in intervention group (p=0.000,95%CI: 1.61 - 4.41). The mean duration of hospital stay was 9.02±7.83SD days in the control group and 8.85± 7.12 SD days among the intervention group (p=0.85). Predictors of mortality were birth weight of ≤ 1200g (AOR=2.6; 95%CI: 1.18-5.85) and HIE score of ≥ 15 (AOR=18.12; 95% CI: 4.0 -82.29) among neonates with VLBW and HIE respectively.

Conclusion: Early feeding using mother's milk by oral mucosal colostrum or minimal enteral nutrition was not associated with increased NEC and mortality in neonates with VLBW and HIE, but this study was underpowered to measure these safety outcomes. Neonates who received early feeding significantly regained birth weight earlier than those with delayed feeding. Early feeding did not shorten duration of hospital stay. Birth weight ≤ 1200g and HIE score of ≥ 15 were independent predictors of mortality among neonates with VLBW and HIE respectively.

Recommendation: A randomized study with large sample size and higher power is recommended to further confirm the safety early feeding among neonates with VLBW and HIE in our settings. However, early provision of breast milk among neonates with VLBW and HIE promotes early weight gain, hence health workers should encourage mothers on breast feeding to promote growth and minimize hospital stay.

MUHTASARI

Utangulizi: Ulishaji wa watoto wachanga wenye uzito mdogo sana na wanaoumwa sana mara nyingi unachelewa kwa sababu ya kutotengamaa kwa mifumo yao ya mwili hivyo kuwafanya wawe na hatari kubwa ya seli za ukuta wa utumbo kufa hivyo kuharibu ukuta wa utumbo (NEC) na vifo vya watoto wachanga. Hii inawanyima watoto kupata faida zitokanazo na virutubisho vilivyomo katika maziwa ambayo mama anatoa mara baada ya kujifungua hivyo kuwaongezea watoto wachanga matatizo mabalimbali ya kiafya ikiwa ni pamoja na maambukizi ya vijidudu vya magonjwa kwenye mfumo wa damu, kudumaa katika ukuaji wa mwili na akili na hata kifo. Kumpa mtoto mchanga maziwa kidogo kidogo kwa njia ya matone mdomoni au kwenye mfumo wa chakula ni njia mbadala zinazoweza kutumika ili kuwahi kulisha watoto wachanga wenye uzito mdogo sana au wanaoumwa sana bila kuwa na madhara yoyote yatokanayo na ulishaji. Lakini hizo njia hazitumiki katika wodi nyingi za watoto wachanga hivyo kusababisha ucheleweshaji wa kuwalisha watoto ambao mifumo yao ya mwili haijatengemaa na kuwasababishia ongezeko la vifo na matatizo mengine ya kiafya.

Lengo kuu la utafiti: Kutambua matokeo ya kuwahi kuwalisha watoto wachanga maziwa ya mama ukilinganisha na kuwaacha bila kuwapa maziwa ya mama hadi mifumo yao itengamae kwa watoto wachanga waliozaliwa na uzito mdogo sana pamoja na wanaoumwa sana waliolazwa katika hospitali za rufaa za mkoa wa Dar es Salaam kuanzia mwezi Oktoba 2018 hadi Aprili 2019.

Mbinu: Utafiti ulifanyika kwa awamu mbili, Awamu ya kwanza ilikuwa ni kwa ajili ya kukusanya taarifa ya matokeo ya kuchelewa kuwalisha watoto wachanga wenye uzito mdogo sana na wanaoumwa maziwa ya mama na awamu ya pili matokeo ya kuwahi kuwalisha maziwa ya mama. Uchunguzi ulifuatilia watoto wachanga waliolazwa katika hospitali ya Temeke, Amana na Mwananyamala kuanzia mwezi Oktoba 2018 hadi Aprili 2019. Watoto wote waliokidhi vigezo vya kushiriki walikaribishwa kushiriki kwenye utafiti. Jumla ya watoto wachanga 292 ambao mama zao walitoa ridhaa walishiriki katika utafiti. Watoto 163 walisajiliwa awamu ya kwanza na 129 awamu ya pili. Watoto wote walioshiriki utafiti huu walifuatiliwa kuanzia siku ya kulazwa hadi siku ya mwisho ya kukusanya taarifa ambayo ni

ruhusa, kifo, kutimiza siku 28 za maisha akiwa bado amelazwa, rufaa au kuondoka wodini bila ridhaa ya daktari. Watoto ambao ukuta wa utumbo uliharibika (NEC) au waliofariki walihesabiwa na kurekodi siku hiyo, vilevile siku ya kufikisha uzito wa kuzaliwa nao na ambazo mtoto amelazwa wodini zilihesabiwa na kutathminiwa.

Ukokotoaji wa takwimu: Tulitumia mchanganuo mbalimbali ili kukokotoa takwimu ikiwa ni pamoja na asilimia kutoa taarifa za kuharibika kwa ukuta wa utumbo (NEC) na kifo, wastani kwa ajili ya umri mtoto alipofikia umri aliozaliwa nao na siku alizokaa wodini. Tulitumia kiwango cha uwiano kutambua viashiria vya vifo vya watoto wachanga kwa kutumia mfumo wa kielektroniki wa SPSS.

Matokeo ya utafiti: Jumla ya watoto wachanga 292 walisajiliwa katika utafiti huu, asilimia 55.8 walisajiliwa awamu ya kwanza na asilimia 44.1 awamu ya pili. Kati yao asilimia 55.5 walikuwa waliochelewa kulia wakati wanazaliwa na 44.5 wenye uzito mdogo sana. Kwa ujumla watoto wanne sawa na asilimia 1.4 walipata tatizo la kuharibika ukuta wa utumbo(NEC), katika awamu zote mbili, awamu ya kwanza watatu na awamu ya pili mmoja. Pia asilimia 40.8 ya watoto walifariki ikiwa ni asilimia 41.7 awamu ya kwanza na 39.5 awamu ya pili. Wastani wa muda wa kufika uzito ambao mtoto alizaliwa nao ulikuwa ni siku 11 kwa awamu ya kwanza na siku nane awamu ya pili. Wastani wa muda wa kukaa wodini ilikuwa ni siku 9 kwa awamu ya kwanza na 8.8 awamu ya pili. Viashiria vya vifo vilikuwa ni kuzaliwa na uzito chini ya gramu 1200 kwa watoto wenye uzito mdogo sana na HIE sawa au zaidi ya 15 kwa watoto waliochelewa kulia wakati wa kuzaliwa.

Hitimisho: Kuwahi kuwalisha watoto wachanga wenye uzito mdogo sana na wanaoumwa sana maziwa ya mama kwa njia ya matone mdomoni au kiwango kidogo kikiongezwa taratibu hakukusababisha ongezeko la kuharibika ukuta wa utumbo (NEC) au vifo. Watoto waliowahi kupewa maziwa ya mama mapema walifikisha uzito waliozaliwa nao mapema zaidi kuliko wale waliochelewa kupewa maziwa ya mama. Kuzaliwa na uzito chini ya gramu 1200 na HIE sawa au zaidi ya 15 ni viashiria vya vifo kwa watoto wachanga.

Mapendekezo: Utafiti mwingine ambao utahusisha watoto wachanga wengi unahitajika ili kuweza kubaini kama ulishaji mapema maziwa ya mama watoto wachanga wenye uzito mdogo sana na waliochelewa kulia wakati wa kuzaliwa unaongeza uwezekano wa kuharibika kwa ukuta wa utumbo (NEC) na matatizo mengine ya kiafya katika eneo letu. Hata hivyo, watoto wachanga wakipewa maziwa ya mama mapema yanasaidia kuongeza uzito mapema, kwa hiyo wahudumu wa afya wawahimize akina mama kunyonyesha watoto mapema.

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LIST OF ABBREVIATIONS

AREDF	-	Absence/reversal of end diastolic flow
DSMB	-	Data safety management board
GALT	-	Gut-associated lymphoid tissue
GIT	-	Gastrointestinal tract
HIE	-	Hypoxic ischaemic encephalopathy
IRB	-	Institution review board
IUGR	-	Intrauterine growth restriction
MALT	-	Mucosal associated lymphoid tissue
MEN	-	Minimal enteral nutrition
NGT	-	Nasogastric tube
NEC	-	Necrotizing enterocolitis
NICU	-	Neonatal intensive care unit
NPO	-	Nil per oral
OMC	-	Oral mucosal colostrum
PI	-	Principal investigator
RCT	-	Randomized controlled trial
SGA	-	Small for gestational age
TDHS-MIS	-	Tanzania Demographic and Health Survey and Malaria Indicator Survey
TPN	-	Total parenteral nutrition
VLBW	-	Very low birth weight
WHO	-	World Health Organization

DEFINITION OF TERMS

Hypoxic ischaemic encephalopathy (HIE): Full term neonates with perinatal asphyxia and Thompson score > 10 during admission

Necrotizing enterocolitis (NEC): defined using clinical and radiological features based on modified Bell's staging criteria. A neonate was considered having NEC if had Bell's criteria stage ≥2A.

Very low birth weight (VLBW): Birth weight between 1000 -1500grams

Control group: neonates who were kept NPO soon after birth, and started feeding after stabilization

Intervention group: Neonates who received breast milk through Oral mucosal colostrum or minimal enteral nutrition within 24 hours of life.

Study end point: End points of data collection in this study were discharge, reached 28 days of life while hospitalized, death, referral to tertiary hospital or discharged against medical advice.

Outcomes: The primary outcome was occurrence of necrotizing enterocolitis and secondary outcomes were mortality, duration of regaining birth weight and hospital stay.

CHAPTER ONE

1.0 INTRODUCTION

1.1 Background

Neonatal period is a critical time for human development due to transition from intrauterine (dependent) life to extra-uterine life. During this time, newborns undergo physiological and anatomical changes for adopting to the new environment (1). Comprehensive care for improving survival is important because this is the most vulnerable time. In 2016, approximately 2.6 million children died in the first month of life with 75% of deaths occurring in the first week of life (2). Early initiation of breastfeeding is one of the effective interventions in decreasing mortality, improve growth and neurodevelopment outcomes among neonates (3). There is high nutritional demand during the neonatal period due to rapid growth and brain development, therefore it is important to provide optimal nutrition in order to prevent extra- uterine growth restriction (4). WHO recommends that, breastfeeding should be initiated within the first hour of life, but in Tanzania only 51% receive breastfeeding within 1st hour of life (5). WHO also recommends initiating 10ml/kg per day of enteral feeds to VLBW infants, preferably expressed breast milk, starting from the first day of life (6). Most countries including Tanzania adopted this feeding regimen but early feeding was not yet implemented in most of the neonatal intensive care units.

During the first few days after birth, colostrum is produced; it is rich in immune-protective and growth factors such as immunoglobulin A (IgA), Lactoferrin, and epidermal growth factor and has the potential to modulate the infant's immune system, especially in preterm infants (7–9). Beginning breast milk immediately after birth ensures that the newborn receives the "first milk" (colostrum), the baby's first "immunization. Early enteral feeding promotes intestinal growth, maturation of intestinal enzymes, increase intestinal motility, perfusion, and hormonal responses (7,8). However, early initiation of breastfeeding is a challenge for neonates with very low birth weight (VLWB) and hypoxic ischaemic encephalopathy (HIE) because of their physiological and haemodynamic instability. They are usually kept nil orally while receiving intravenous fluid for the first 48-72 hours of life in low resource settings while parenteral

nutrition is provided only in well-equipped facilities (4,10). Despite being the most vulnerable group they are not benefiting from immunological role of colostrum and hence are likely to have a high morbidity and mortality. Other feeding options are available in order to provide early enteral feeding to VLBW and critically ill neonates instead of keeping them nil per oral. Early enteral feeding can be safely administered using trophic feeding (minimal enteral nutrition) or oral mucosal colostrum administration.

Minimal enteral nutrition (MEN) involves providing small amount of enteral feeds (starting with 10 ml/kg/ day) preferably expressed breast milk, starting from the first day of life, with the remaining fluid requirement met by intravenous fluids. The volume of enteral feeds is increased slowly while reducing the amount of intravenous fluid until full enteral feeding is achieved (10,11). Minimal enteral feeding is a non-nutritive feeding aiming at priming the gastric intestinal tract. It reduces the incidence of NEC, reduces the duration of achieving full enteral feeding and neonates regain birth weight early (12,13). On the other hand, administration of oral mucosa colostrum (OMC) provides the benefits of colostrum even in the critically ill and preterm neonates who cannot yet tolerate enteral feeding. Small volume of colostrum (0.1-0.2mls) is placed in the buccal cavity by a syringe or swab. It does not require swallowing of colostrum but allows it to act locally and to be absorbed by the buccal mucosa but provide more beneficial effects than delayed feeding (8,9,14).

Although evidences have shown that, modified neonatal feeding approach by OMC/MEN have more benefits than keeping them nil per oral, it is unclear if the benefits reported in these studies apply to our settings. The differences in study population in terms of genetics, causes of VLBW and differences in infectious disease prevalence and health system factors may lead to differences in how neonates respond to early enteral feeding. Therefore, using a quasi-experimental design we aim to determine the effect of early feeding using mother's milk on the early neonatal outcomes compared to nil oral feeding amongst neonates with VLBW and hypoxic ischaemic encephalopathy in regional hospitals in Dar es Salaam.

1.2 Problem statement

Early feeding within the first hour of life can be one of the cost-effective methods in reducing NEC and other short and long-term health complications including mortality in neonates with VLBW and HIE. The norm in management of these neonates is delaying the onset of enteral feeding, which is considered the "standard of care" based on their physiological and haemodynamic instability. As a result neonates with VLBW and HIE experience major protein and energy deficits during hospitalization in neonatal intensive care units (NICUs). The 2017 Tanzania standard treatment guidelines and essential medicines list for children and adolescents recommends starting trophic feeding in VLBW <1500g, for both stable and unstable neonates soon after delivery and describes feeding advancement so that the neonate can reach full feeds of 150mls/kg by second week of life.

Despite these guidelines on early enteral feeds the fear of NEC is mentioned as a major barrier for initiation and progression of early enteral feeds among neonates with VLBW and HIE. Furthermore, because the guideline does not describe feeding volumes, frequency and volume advancement among neonates with HIE, variation in practice in facilities that have adopted the new guidelines have been reported. This has resulted in most neonatal units continuing with the nil per oral feeding regimen for 48-72 hours for unstable neonates.

1.3 Rationale

Findings from this study will provide baseline information on possible positive effects of early infant feeding in our setting. The study will also shed light on what is the best feeding modality between minimal enteral nutrition or oral mucosal colostrum, the feeding volumes and frequencies for unstable neonates admitted at regional hospitals in Dar es Salaam. Our findings will generate local evidence to inform clinicians and to improve feeding guidelines for unstable neonates.

1.4 Conceptual framework for effects of early neonatal feeding among neonates with VLBW and HIE

Delayed initiation of enteral feeding leads to a reduced functional adaptation and perfusion in the gut hence ischemia and damage of gut mucosa in haemodynamic unstable neonates. This causes dislocation of normal gut flora which invade gastrointestinal wall and induce inflammatory response leading to gut necrosis (NEC). Damage of gut mucosa and disturbance of gut normal flora cause colonization of the gut by pathogenic organisms which worsens NEC. Necrotizing enterocolitis can either lead to mortality or prolong hospital stay and duration of regaining birth weight among survivors. Both maternal and neonatal co-morbidities contribute to the reduction of gut perfusion and ischemia which further increases the risk of NEC in unstable neonates. Early feeding using mother's milk improves gut perfusion, promotes gut maturation, GIT motility, enzyme secretion and response. This prevents ischemic injury to the gut mucosa which later prevents inflammatory response and dislocation of normal flora and as a result decreases NEC. Early feeding also stimulates growth of MALT (mucosal associated lymphoid tissue) and GALT (Gut-associated lymphoid tissue) hence improve immune system and protect the gut from being colonized by pathogenic organisms. Early feeding also improves feeding tolerance and hence rapid weight gain and shortens duration of hospital stay.

This study was assessing effects of early neonatal feeding using mother's milk among hemodynamically unstable neonates. The primary outcome was the incidence of NEC and secondary outcomes were neonatal mortality, duration of regaining birth weight and duration of hospital stay.

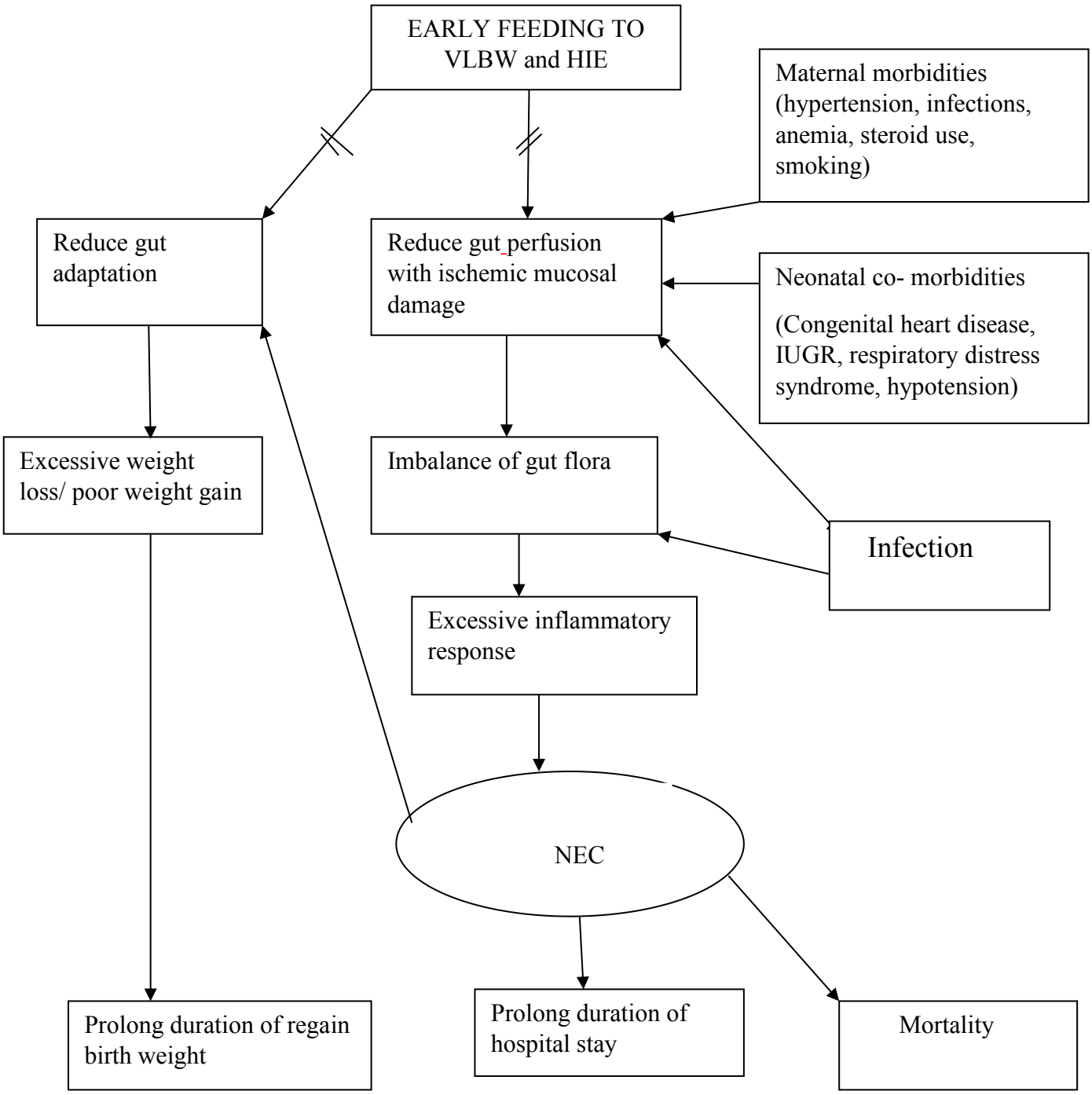


Figure 1: Conceptual framework for effects of early neonatal feeding among neonates with VLBW and HIE

1.5 Research questions

1. Is there any difference in the proportion of NEC among neonates initiated on early feeding versus those on nil orally standard feeding practice?
2. Is there any difference in the mortality rate among neonates initiated on early feeding versus those on nil orally standard feeding practice?
3. Will early feeding using mother's milk shorten duration of regaining birth weight among neonates with VLBW and HIE?
4. Will early feeding using mother's milk shorten duration of hospital stay among neonates with VLBW and HIE?

1.6 Objectives

1.6.1 Broad objective

To determine effects of early feeding using mother's milk on neonatal outcomes compared to nil orally standard feeding practices amongst neonates with very low birth weight and hypoxic ischaemic encephalopathy admitted at regional referral hospitals in Dar es Salaam

1.62 Specific objectives

1. To estimate the proportion of necrotizing enterocolitis in neonates with VLBW and HIE who are on early feeding and those on nil oral feeding practice in regional hospitals in Dar es Salaam
2. To compare the mortality rate of VLBW and HIE neonates on early feeding versus those on nil oral feeding practice in regional hospitals in Dar es Salaam
3. To determine the duration to regaining birth weight among neonates with VLBW and HIE who received early feeding versus those on nil oral feeding practice in regional hospitals in Dar es Salaam
4. To determine the duration of hospital stay among neonates with VLBW and HIE who are on early feeding versus those on nil oral feeding practice in regional hospitals in Dar es Salaam

CHAPTER TWO

2.0 LITERATURE REVIEW

2.1.0 Risk of necrotizing enterocolitis (NEC).

Necrotizing enterocolitis (NEC) is the most common gastrointestinal emergency in neonates, with high morbidity and mortality in neonatal intensive care units. More than 90% of all cases of necrotizing enterocolitis occur in VLBW preterm infants. Full term neonates with other pathological conditions including: those with HIE, SGA/IUGR, cyanotic CHD, polycythemia, respiratory insufficiency and early neonatal sepsis also have an increased risk of NEC. About 90–95% of neonates developed NEC after introduction of enteral feeding and formula milk further increases the risk (15–17). Pathogenesis of NEC involves multifactorial processes including gut ischaemia and injury with subsequent inflammatory reactions of intestinal wall. Inflammatory damage of mucosa causes invasion of pathogenic bacteria and subsequent release of inflammatory mediators like tumor necrosis factor Alpha, IL-1, IL-6 and IL-8, which worsen inflammatory process. Formula milk predisposes to alteration of bacterial colonization in the gut causing replacement of normal flora by pathogens. Invasion of gut by pathogens cause exaggerated mucosal inflammatory cascade which increases the risk of NEC.

2.1.1 Necrotizing enterocolitis in neonates with very low birth weight (VLBW)

Immature gut in preterm infants predisposes them to NEC, which leads to delay in introduction of enteral feeds among very low birth weight (VLBW) and extremely low birth weight neonates. But delay in enteral feeding leads to diminished functional adaptation of the gut, which contributes to feeding intolerance and increase in neonatal morbidities. A Cochrane analysis of seven randomized controlled trials involving VLBW and SGA neonates showed that delayed introduction of enteral feeds does not reduce the risk of NEC (13). A randomized controlled trial on early versus delayed trophic feeding among 170 neonates with VLBW observed only one case of NEC in each group (18). Another study done in Turkey among 297 VLBW preterm babies who were intubated reported that the proportion of NEC was 6.2% in those who received feeding early during intubation compared to 7.2% in those received later

after intubation (19). Also Romanio *et al* also observed the proportion of NEC to be 4% in neonates who received colostrum priming and 2% in the non-colostrum group (20). In all studies there was no significant difference in NEC among early and delayed feeding group.

2.1.2 Necrotizing enterocolitis in neonates with VLBW due to intrauterine growth restriction

In neonates with IUGR, blood flow is preserved for vital organ function (brain, cardiac and adrenal gland) while it is reduced in other visceral organs including the gut. Reduced blood flow to the gut might causes hypoxic-ischaemic damage of the intestinal mucosa predisposing neonates with IUGR to feeding intolerance and NEC. If prematurity is complicated with IUGR, the risk of NEC is even higher. During first few days of life there is gradual recovery of intestinal perfusion and hence enteral feeding is usually withheld until adequate gut perfusion occurs to prevent feeding intolerance and NEC. Despite the increased risk of NEC in neonates with IUGR, four randomized trials on early versus delayed enteral feeding for preterm growth-restricted infants gave contradictory findings and found no significant difference in the incidence of NEC between early and delayed enteral fed neonates (21–24). Two of the studies reported a slightly higher incidence of NEC in the early feeding group than delayed feeding group 18% Vs. 15%, and 15% Vs. 9.5% respectively (22,23). However, another two studies reported a high incidence of NEC in the delayed feeding group than the early feeding group (12.9%Vs 9.5%) (21,24). One of the studies concluded that birth weight was an independent factor for development of NEC rather than the time of initiating MEN(24). Neonates with NEC in these trials were delivered at significantly earlier gestational age and had lower birth weights. Hence, the high incidence of NEC in these neonates may be due to cumulative effects of both prematurity and IUGR since both of them are associated with LBW and increased risk of NEC.

2.1.3 Necrotizing enterocolitis in neonates with hypoxic ischaemic encephalopathy

Impaired gut blood flow and presence of intraluminal milk in neonates with HIE facilitates an inflammatory cascade and gastrointestinal necrosis increases the incidence of NEC. Enteral feeding in neonates with moderate to severe HIE is usually withheld for 3 to 5 days in most

neonatal intensive care units (NICUs) and intravenous fluid or TPN is used while GIT is recovering from ischemic injury. However, delayed enteral feeding decrease GIT motility, impairs enzyme release and gut adaptation. There is a wide variation of feeding practices among children with HIE due to fear of NEC, safety and feasibility and no universal feeding guideline is being used (25). A cohort study on enteral feeding among neonates with HIE receiving therapeutic hypothermia showed that no infants developed NEC between those with early or delayed enteral feeding (26). Despite that, therapeutic hypothermia has a protective effect on the gut in neonates with HIE, early enteral feeding also has stimulatory effects in the gut and can have contributory effects on reduction of NEC. It is difficult to estimate magnitude of NEC in neonates with HIE receiving early enteral feeding due to few studies and wide variation of feeding practices in various NICUs.

2.1.4 Feeding advancement and necrotizing enterocolitis

Advancement of enteral feeding in haemodynamic unstable neonates poses a challenge on feeding progression on these neonates. Rapid advancement of progressive enteral feeding was believed to be associated with increased incidence of NEC. A multi-centre case control study in preterm neonates indicated rapid advancement of enteral feeding was associated with a higher incidence of NEC (27); but a Cochrane review involving 10 RCTs with a total of 3753 infants showed that slow advancement of progressive enteral feeding did not reduce incidence of NEC but prolonged the time of achieving full enteral feeding (28).Two other similar studies also found that rapid advancement of enteral feeding did not increase the incidence of NEC in preterm infants (29,30).

2.2 Risk of mortality

Early initiation of breastfeeding in neonates is a key determinant for survival and development of all neonates (31,32). Most of the neonatal deaths that occur during the first week of life can be prevented by early initiation of breast feeding. Breastfeeding must be initiated within first hour of life as the risk of neonatal deaths is directly related to time of initiation of feeding (32). A study done in Indonesia showed that LBW neonates who had delay in receiving breastfeeding within an hour of life had a 2.9 times greater risk of death compared to those

neonates who received breastfeeding within one hour of life (31); while in Ghana neonates were 2.5 times more likely to die when breastfeeding initiation began after 24 hours (33). Approximately one-fifth (22%) of all neonatal deaths could be avoided if breastfeeding was initiated within the first hour of life for all neonates (33). A systematic review and meta-analysis study found a 33% increase in neonatal mortality among infants who initiated breastfeeding 2–23 hours of life while further delay more than 24 hours lead to increased mortality by 2.19- fold (34).

Recently researchers explored more on the role of trophic feeding/OMC on reduction of neonatal mortality among high risk neonates including those with VLBW. A randomized control trial by Celik et al in Turkey on early versus delayed enteral feeding among VLBW neonates who were intubated reported a mortality rate of 31.1% among neonates with delayed feeding and 26.1% in the early feeding group (19). Another randomized controlled trial by Tewari et al in India on early compared to delayed feeding among preterm neonates with IUGR and Absence/reversal of end diastolic flow (AREDF) observed mortality rate of 9.5% Vs 14.3% in early and delayed feeding groups respectively (21).

The burden of neonatal mortality in Tanzania is still high, perinatal asphyxia and VLBW are the leading cause of morbidity and mortality. A retrospective cohort by Mmbaga *et al* on cause-specific neonatal mortality in the neonatal care unit in Northern Tanzania found 45.7% of all neonatal deaths were due to perinatal asphyxia while prematurity contributed to 35.1% of all deaths (35). There is limited studies on effects of early feeding in neonates with HIE, despite that neonates with HIE pose feeding challenges in NICUs due to their haemodynamic instability.

2.3 Duration of regaining birth weight

Most neonates admitted in NICUs face postnatal growth failure(36,37) and inadequate postnatal feeding is the major contributing factor. Preterm infants and critically ill neonates experience major protein and energy deficit while admitted in NICUs (36). Delayed feeding can cause significant weight loss greater than the normal 10% of the birth weight which later on prolongs time of attaining birth weight and failure of catching up growth. A cohort study

done in Iran on early versus late trophic feeding in VLBW preterm infants indicated that neonates who received early trophic feeding regained birth weight 7days earlier than those with delayed trophic feeding (13.75±5.21 vs. 20.53±6.31; p<0.001) (18). In a randomized clinical trial SGA neonates who received early feeding had significant higher weight gain at time of discharge than those with delayed feeding (23). Another RTC on early vs late enteral feeding on preterm IUGR neonates with abnormal antenatal Doppler reported that the early fed group regained birth weight earlier than delayed group with median time of 13(12-17) and 19(17-20) days respectively (21). Optimization of nutritional supply after establishing enteral feeding is important in order to prevent further weight loss, which prolongs duration of regaining birth weight. Despite several evidences that early feeding shortens duration of regaining weight, one study observed no significant difference on median time of regaining weight between early and delayed fed neonates (13 Vs 14 days) (24). Several studies evaluating effects of early feeding on weight gain have been done in VLBW/SGA neonates, however, there is limited evidence on its role among neonates with HIE.

2.4 Duration of hospital stay

Most VLBW and critically ill neonates are hospitalized for long periods of time (>7days) due to failure to establish oral feeding, feeding intolerance, NEC, poor weight gain and co-morbidities like sepsis (38). Long duration of hospital stay may predispose them to hospital-acquired infections, which further prolong duration of hospital stay. Early introduction of enteral feeding is an important strategy on improving feeding tolerance, weight gain and neonatal morbidities. A randomized trial on oropharyngeal colostrum administration in extremely premature infants noted significant reduction in the incidence of clinical sepsis in colostrum primed group by 42% (50% vs 92%). Also another randomized trial on early against delayed feeding among SGA found early feeding reduces incidence of late onset neonatal sepsis by 7% (28% vs. 35%) and cholestatic jaundice by 9% (13% vs. 22%). Both MEN and OMC have significant impacts on shortening of duration of hospital stay (18,20). A cohort study done in Iran indicated that early trophic feeding shortens duration of hospital stay by 42%(12.14±8.612 vs. 21.11±1.156) (18). This finding is similar to a randomized clinical

trial on effects of oral colostrum priming in preterm neonates (< 32weeks) whereby oral colostrum priming reduced duration of hospital stay by 16 days (20). Another study in Florida-USA on enteral feeding as an adjunct to hypothermia in neonates with hypoxic-ischaemic encephalopathy also found a significant reduction on duration of hospital stay among neonates with HIE who received early enteral feeding (15±11 vs.24±19 days, $p<0.05$) (39). In most studies neonates stayed in hospital longer than 7days but there was significant reduction on hospital stay among neonates who received early feeds.

CHAPTER THREE

3.0 METHODOLOGY

3.1 Study design

This was a hospital-based, non-blinded, quasi intervention study design using a historical control which aimed at evaluating the effects of early feeding in VLBW and critically ill neonates. This design was selected because it was more robust to detect small to moderate-size effects than other epidemiological study designs. In addition, the investigator had the possibility of allocating the intervention.

3.2 Study duration

The study was conducted over a period of seven months where, three months were used to collect data under the current feeding regimen which is nil orally until after stabilization of VLBW and critically ill neonates. This constitutes the historical control group. The last three months were allocated for early feeding regimen using the WHO standard of feeding in haemodynamically unstable neonates and this constitutes the intervention group. One month was used for training health care workers and research assistants on the early feeding regimen prior to onset of the intervention.

3.3 Study area

This study was carried out in neonatal units at three regional referral hospitals in Dar es Salaam Tanzania [Temeke, Amana and Mwananyamala]. These hospitals serve as the primary referral centres receiving patients from health centers located in the respective municipality. Dar es Salaam region has approximately 120,000 deliveries per year. In 2016, the three regional hospitals had 37,733 deliveries and about 8, 546 neonates including those born in these hospitals and referred cases were admitted in the neonatal units. Among the admitted neonates, 937 (11%) of them died. The average admissions per month were 420 neonates at Temeke hospital, 320 neonates at Amana hospital and 280 neonates at Mwananyamala hospital. The leading causes of admission were prematurity with VLBW, neonatal sepsis, HIE

and anaemia. Neonatal units in these hospitals have an average of 6 pediatricians, 9 medical officers, 26 nurses and 7 medical attendants.

3.4 Study population

All neonates admitted at the neonatal care units at the three regional referral hospitals Amana, Mwananyamala and Temeke from July 2018 to February 2019.

3.4.1 Inclusion criteria:

- Neonates with VLBW (1000-1500g)
- Term neonates with perinatal asphyxia (HIE score>10)
- Age < 24hours during admission

3.4.2 Exclusion criteria:

- Neonates born to HIV positive mothers who opt not to breastfeed
- Neonates with features suggesting gut malformation such as imperforate anus, esophageal atresia and duodenal atresia who cannot be fed orally until after surgical intervention
- Referred neonates/admitted in the neonatal wards after 24 hours of life
- Neonates whose mothers declined consent

3.5 Sample size

The sample size was calculated using the formula for comparative study of two population proportions- binary outcome (40) ;

$$n=\frac{[Z_{\frac{\alpha}{2}}\sqrt{2\bar{P}(1-\bar{P})}+Z_{\beta}\sqrt{P_1(1-P_1)+P_2(1-P_2)}]^2}{[P_1-P_2]^2} \text{ where}$$

$$\bar{P}=\frac{P_1+P_2}{2}$$

Whereby n is the number of subjects in one group

Z = value for the confidence level

α = value for the type 1 error: 0.05($Z\ \alpha/_2$ =1.96)

β = value for type II error ($Z_1\beta$=0.84)

P = estimated proportion of NEC in the control group. In this case 12.9% taken as prevalence of NEC in the control group from a study by Abdelmaaboud *et al* in Quatar in 2009 to 2011 (24).

P2 = 2.6% (Expected proportion of NEC after introduction of early feeding)

Hypothesis: Introduction of early feeding will lead to reduction in the proportion of NEC by 80% (from 12.9% to 2.6%)

Therefore, N=106.

Sample size = n×2 equals to 212.

After adjusting for a 20% non-response rate, the minimum estimated sample size was 254 neonates.

A total of 292 neonates were enrolled in this study (163 neonates in control group and 129 in intervention group). A total of 119(41%) neonates fromTemeke, 93(32%) from Amana and 80(27%) from Mwananyamala hospital whereby proportion of neonates from each hospital was calculated based on number of admissions in each hospital.

3.6 Sampling technique

All neonates admitted in neonatal care unit during the study period were screened for eligibility. Those who met inclusion criteria were consecutively enrolled in this study until sample size obtained. Historical controls were neonates recruited during the first three months using NPO feeding regimen and intervention group were neonates recruited during the last three months using early feeding regimen.

3.7 Study outcomes

3.7.1 Primary outcome

Necrotizing enterocolitis

3.7.2 Secondary outcomes

Mortality, duration of hospital stay and duration of regaining birth weight

3.8 Study variables

3.8.1 Independent variables

The independent variable in this study was feeding

3.8.2 Dependent variable

The dependent variables included: incidence of NEC, neonatal mortality, time to regain birth weight, duration of hospital stay, gestational age and HIE score.

3.9 Data collection tools

Case report forms were used to collect information including socio-demographic information and short term outcomes of neonatal feeding. Feeding and monitoring charts were developed and attached to each participant's file recording and monitoring of feeding volume, vital signs and feeding adverse events. Other tools were;

3.9.1 Thermometer

Axillary body temperature was measured using a digital clinical thermometer (Omron). The digital thermometer was placed in the axilla and two temperature readings were recorded taken two minutes apart. Body temperature of more or equal to 38.5°C was regarded as febrile while temperature less than 36.5°C was regarded as hypothermia.

3.9.2 Weighing scale

Body weight was measured using a SECA digital weighing scale (German) and measured to the nearest 10grams with neonates unclothed. The weighing scale was calibrated to zero daily before weighing the neonates.

3.9.3 Pulse oximeter

Pulse oximeter was used to measure pulse rate and oxygen saturation. Pulse rate was expressed in beats/minute and oxygen saturation in percentages (%).

3.9.4 Ballard's score chart

Was used for assessment of the gestational age for physical and neurodevelopment maturation of VLBW neonates during admission.

3.9.5 Thompson score chart

Was used for assessment of HIE among term neonates with perinatal asphyxia during admission

3.9.6 Laboratory investigations

By using aseptic technique 2mls of blood was collected through venipuncture for complete blood count (CBC).

3.9.7 Radiological test

Plain abdominal X-rays were done in neonates who presented with abdominal distension, bilious vomiting and diarrhea with blood to assess if they had NEC.

3.10 Data collection procedures

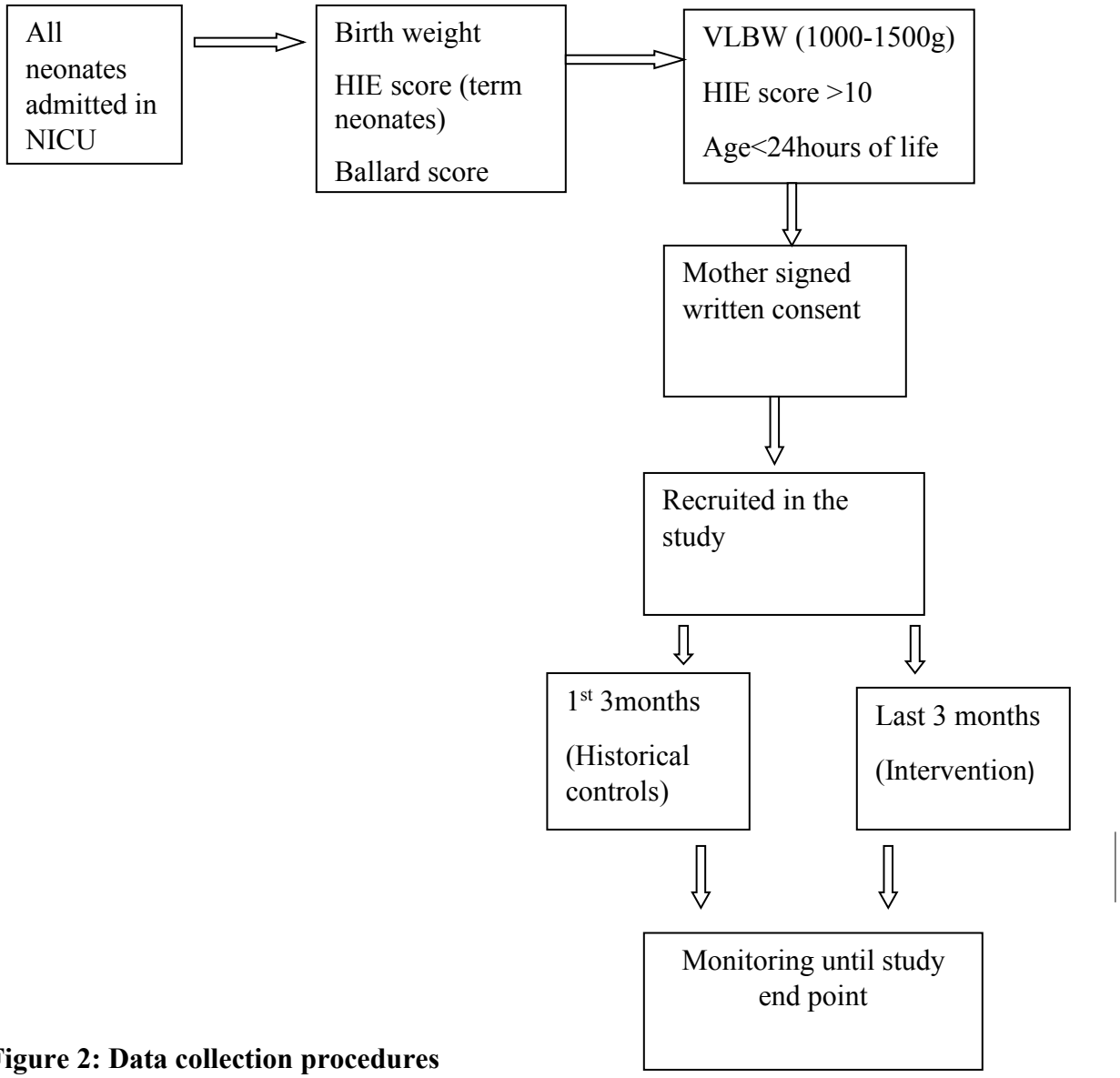


Figure 2: Data collection procedures

3.11 Training of research assistants

A total of 20 research assistants were trained on the recruitment of study participants, assessment for eligibility criteria, neonatal assessment during recruitment and throughout the study, identification and management of feeding adverse events, filling the case report form and use of the monitoring tools. They had a one day session on the general overview of the data collection procedures and two days practical sessions which were done at CCBRT**.** After

training post test was done and 12 participants with highest score were selected as research assistants for data collection in this study. Also the PI reserved contacts of other 5 trainees for backup in case of any emergency which may interrupt data collection procedures.

A Pilot study was done before the study involved 10 VLBW and 10 neonates with HIE to assess data collection tools. However, the data from the pilot study were not included in the final report.

3.12 Orientation of feeding protocol to neonatal care units health care workers

Before collection of baseline data (control), a meeting was done with neonatal care unit workers from the three hospitals for reviewing the feeding guideline, HIE scoring and essential newborn care to ensure uniformity in all hospitals. Also before intervention orientation was done for three days and involved a brief overview on the feeding protocol, the benefits of early feeding compared to delayed feeding and feeding techniques. This was followed by surveys twice per week in each health facility assessing acceptability of health workers on the new recommended feeding regimen.

3.13 Data collection procedure

3.13.1 Intervention group

Study participants were enrolled during admission. Body weight, gestational age (Ballard score), HIE score (using Thompson HIE score) and vital signs were recorded. Stable neonates were started with 10mls/kg/day MEN through NGT within the first 24hours and advanced at the rate of 20mls/kg/day from the second day of life. OMC was administered to all unstable neonates by trained research assistants, 0.4mls of colostrum (0.2mls in each cheek) in the oral mucosa using 2.5mls syringes. This was followed by inserting a 5Fr/10Fr nasogastric tube (NGT) MEN starting with 10mls/kg/day and advanced at the rate of 20ml/kg per day within 48hours of life until reaching full enteral feeding of 150mls/kg/day. OMC was continued in neonates with NGT feeding until the neonates started oral feeding. Both OMC and MEN were provided every two/three hours depending on feeding protocol of the facility using 5mls or 10mls syringes based on the amount of milk administered to the neonates. Neonates received

all other standard of care including: intravenous fluids, antibiotics and oxygen therapy according to the demand. OMC was administered by research assistants and trophic feeding initially administered by a research assistant while training mothers on how to continue feeding after the neonates had stabilized.

Vital signs were taken and recorded before feeding and 10 minutes after feeding in the first three days after initiation of feeding or until stable for neonates who are on CPAP/oxygen therapy. Regular monitoring and reporting of changes in skin/mucus membrane color, breathing pattern, respiratory rate, heart rate, excessive cough, vomiting/aspiration during and after feeding was also done. If a neonate developed apnea, cyanosis, aspiration, an increase in RR>80breaths/min and PR> 200beats/minutes, was considered of having feeding adverse event. Feeding was stopped until signs of respiratory distress subsided while the neonate continued with intravenous fluid and closely monitored. Mothers were also trained on identifying these danger signs and reported to a nursing staff or research assistant immediately.

Neonates were monitored for features suggestive of NEC, including: abdominal distension, bilious vomiting and bloody diarrhea. Feeding was interrupted in all participants who presented with features suggestive of NEC. A complete blood count (CBC) and plain abdominal X-ray were performed to evaluate whether the symptoms were due to NEC or other causes and X-rays were interpreted by qualified radiologists. A neonate with confirmed NEC was managed by the attending paediatrician following standard guidelines for management of NEC. Neonates with no radiological features of NEC were also managed according to the diagnosis arrived at after laboratory investigations.

3.13.2 Control group

Study participants were enrolled during admission, body weight, gestational age (Ballard score), HIE score (using Thompson HIE score) and vital signs were recorded. They received intravenous fluid and were kept on nil orally. Initiation of oral/enteral feeding was based on the decision of the attending clinician after stabilizing the neonates. A 5Fr nasogastric tube (NGT) was used for VLBW <1500g and 10Fr was used for term neonates with HIE for feeding. Daily feeding volume, feeding advancement and intravenous fluid requirements were

calculated by the attending clinician following the current feeding regimen. Research assistants recorded body weight, daily feeding volume; and observed and recorded changes in skin/mucus membrane color, breathing pattern, respiratory rate, heart rate, excessive cough, vomiting/aspiration during and after feeding. They were also monitored for features suggestive of NEC.

If a neonate presented with features suggestive of NEC, complete blood count (CBC) and plain abdominal X-ray were performed to evaluate whether the symptoms were due to NEC or other causes and X-rays were interpreted by two qualified radiologists. The neonate continued with management according to the treatment guideline.

3.14 Quality Assurance

The PI visited each facility twice per week to monitor the data collection progress, and resolve any challenges faced by assistants during data collection. However, the PI also visited the health facilities anytime if a problem requiring urgent intervention had arisen. During these visits the PI assessed for adherence to the feeding protocol and standard operating procedures for data collection by the health care workers and research assistants. The PI also checked if measuring instruments were well calibrated.

X-rays were interpreted by two radiologists, one radiologist from the respective health facility followed by an independent radiologist from Muhimbili national hospital. The PI compared the results, and in case of discordant results both radiologist discussed the results and reached consensus.

3.15 Data safety management

During the intervention, participants' safety was assessed through the monitoring for adverse events by a Data Safety and Monitoring Board (DSMB) comprised of independent reviewers. The DSMB consisted of one pediatrician, an epidemiologist and one biostatistics expert. The DSMB met two weeks after beginning of the intervention. They provided their recommendation on the MUHAS IRB. Adverse events monitored were aspiration/chocking,

bradycardia (<100bpm), tachycardia (HR>200beats/minutes), tachypnea RR>80breaths /minutes, decreased oxygen saturation or apnea within 15minutes after feeding. The DSMB also monitored for any increase in the incidence of NEC and/or mortality resulting from the intervention.

3.16 Data management and analysis

Data was entered, cleaned and analyzed using SPSS version 20. It was an intention to treat analysis. Categorical variables including the proportion NEC and mortality were presented using proportions. Continuous variables - length of hospital stay and duration of regaining birth weight were presented using mean (standard deviation) or median (inter quartile range) depending on whether they are normally distributed or skewed, respectively. Chi-square test or when appropriate Fisher's exact test was used to compare statistical significance in outcomes. Odds ratio (OR) was used to determine association between independent variable (feeding type) and dependent variables (outcomes). The results were considered of statistical significance when P-value was ≤ 0.05.

3.17 Ethical considerations

Institutional ethical clearance was obtained from the Muhimbili University of Health and Allied Sciences Institutional Review Board. Permission to conduct this study was sought from Temeke, Amana and Mwananyamala municipal authorities and the respective hospitals. Mothers of eligible neonates were requested to provide a written informed consent prior to enrolment of their neonates. A mother was free to withdraw her child from the study at any point in the study without fear of negative consequences on the treatment and care of her child. Confidentiality was maintained by use of a study identification number, which could not be linked back to the participants' hospital details. The researcher ensured that all neonates approached during the course of the study continued to receive the standard of care offered in the respective hospitals.

CHAPTER FOUR

4.0 RESULTS

A total of 6473 neonates were admitted and screened for eligibility during the study period. During the first phase 3578 neonates were screened and 217 neonates met inclusion criteria. Of those, 163 neonates participated in this study while 54 were excluded due to various reasons as shown in the diagram below (Figure 1). During the second phase 2895 neonates were admitted and screened for eligibility. And 174 neonates were eligible, among them 129 participated in this study while 46 excluded due to various reasons (Figure 3).

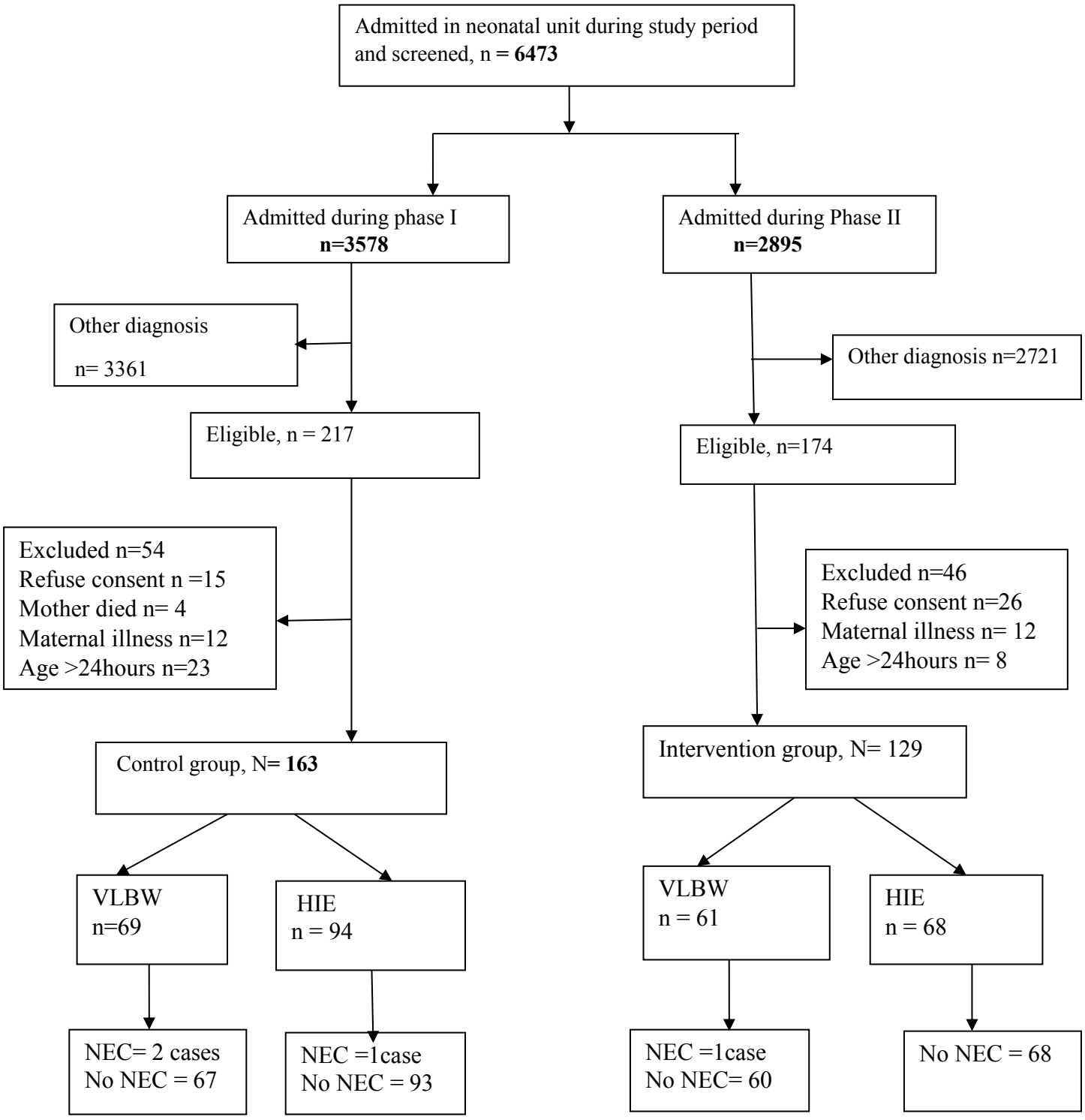


Figure 3: Flow diagram showing enrollment of study participants

4.1 Baseline characteristics of study participants

A total of 292 neonates were enrolled in this study, 55.8% (163) in the control group and 44.2% (129) in the intervention group. Among the study participants, 40.8% (119) were from Temeke hospital, 27.4% (80), Mwananyamala hospital and 31.8 %(93) Amana Hospital. Study participants comprised of 44.5% (130) neonates with VLBW and 55.5% (162) with HIE. Males accounted for 53.4% (156). About half mothers of study participants, 56.8% (166) had primary school education and the majority 77.7% (227) were aged 20-34 years. The two groups were comparable in their baseline characteristics as shown in table 1.

Table 1: Socio-demographic characteristics of the study participants

Variable	**Category**	**Controls N =163**	**Intervention N= 129**	**Total N= 292**	P value
Hospital	**Temeke**	68(41.7)	51(39.5)	119 (40.8)	
	Mwananyamala	46(28.2)	34(26.4)	80 (27.3)	
	Amana	49(30.1)	44(34.1)	93(31.8)	0.761
Sex	**Male**	88(54.0)	68(52.7)	156(53.4)	
	Female	75(46.0)	61(47.3)	136 (46.6)	0.828
Reasons for admission	VLBW	69(42.3)	61(47.3)	130 (44.5)	
	HIE	94(57.7)	68(52.7)	162(55.5)	0.397
Maternal education	**No formal education**	19 (11.7)	14 (10.9)	33 (11.3)	
	Primary school	91(55.8)	75(58.1)	166 (56.8)	
	Secondary school	48(29.4)	35(27.1)	83(28.4)	0.944
	Higher education	5(3.1)	5(3.9)	10 (3.4)	
HIE score	11-14	79(48.5)	61(47.3)	140(47.9)	

	≥15	15(9.2)	7(3.4)	22(7.5)	
	Not applicable	69(42.3)	61(47.3)	130(44.5)	0.41
Weight	≤1200g	33(20.2)	24(18.6)	57(19.5)	
	1201-1500g	36(22.1)	37(28.7)	73(25.0)	
	≥2500	94(57.7)	68 (52.7)	162(55.5)	0.434
Gestational age	27-32weeks	54(33.1)	48(37.2)	102(34.9)	
	33-36weeks	15(9.2)	13(10.1)	28(9.6)	
	≥37weeks	94 (57.7)	68(52.7)	162(55.5)	0.700
Maternal age	< 20years	22(13.5)	13(10.1)	35 (12.0)	
	20 -34years	123 (75.5)	104 (80.6)	227(77.7)	
	≥ 35	18 (11.0)	12(9.3)	30(10.3)	0.559
Parity	Para 1	72 (44.2)	55(42.6)	127(43.5)	
	Para 2	46 (28.2)	29 (22.5)	75(25.7)	
	≥Para 3	45 (27.6)	45(34.9)	90(30.8)	0.333

4.2 Feeding characteristics of study participants

Overall 69.9 %(114) of controls and 96.1 %(124) of intervention started feeding before the study endpoint. Among neonates with VLBW, 53(76.8%) controls and 57 (95.1%) of intervention started feeding while neonates with HIE 61 (64.9%) of controls and 64 (94.1%) of intervention started feeding before study end point. The mean age of initiating feeding was 45.34 ± 21.58SD hours among controls and 8.43 ± 3.02SD hours among the intervention group (p-value = 0.000). VLBW controls started feeding at 38.12 ± 14.08SD hours while the intervention VLBW neonates started at 8.25 ± 3.14SD hours. Among the neonates with HIE, controls started feeding at a mean age of 51.58 ± 25.24SD hours compared to 8.59 ±2.49SD hours in the intervention group. Most of the interventions 74.4% (96) received OMC, and at the study end point 48.8% (42) of the controls and 67.2% (45) of the intervention group were on full breast feeding, table 2.

Table 2: Feeding characteristics of study participants

Variable	Category	Controls N= 163	Intervention N=129	Total (n %)	*p* value
Started feeding before end point	Yes	114(69.9)	124(96.1)	237(81.5)	
	No	49 (30.1)	5 (4.7)	54(18.5)	***0.00***
Mean age started feeding(hours)	All neonates	45.34 ± 21.58SD	8.43 ± 3.02SD hours		***0.00***
	VLBW	38.12 ± 14.08SD	8.25 ± 3.14SD		***0.000***
	HIE	51.58 ± 25.24SD	8.59 ±2.49SD		***0.000***
Feeding method During initiation of feeding	NGT	45(27.6)	6(4.7)	51(17.5)	
	Cup	47(28.8)	19(14.7)	66(22.6)	
	Cup and breastfeeding	22(13.5)	3(2.3)	25(8.6)	
	OMC		96(74.4)	96(32.9)	
	Not applicable	49(30.1)	5(3.9)	54(18.5)	
Feeding modality during study end point	NGT	1(1.2)	0	1(0.7)	
	Cup	6(7.0)	0	6(3.9)	
	Breastfeeding and cup	37(43.0)	22(32.8)	59(38.6)	
	Breast feeding only	42(48.8)	45(67.2)	87(56.9)	

4.3 Proportion of necrotizing enterocolitis (NEC) among the study participants

Overall out of 292 study participants 4(1.4%) had necrotizing enterocolitis**.** Of those with necrotizing enterocolitis, 1.8 %(3) were from the control group and 0.8 %(1) was from the intervention group (p= 0.44, OR= 2.4; 95%CI: 0.25-23.3). Only one neonate from the control group with necrotizing enterocolitis had HIE.

Table 3: Showing the proportion of necrotizing enterocolitis (NEC) among the study participants

	Confirmed NEC		**Total (%)**	**P value, 95% CI**
	YES (%)	**NO (%)**		
Control	3(1.8)	160(98.2)	163(55.8)	*0.44(0.25-23.3)
Intervention	1(0.8)	128(99.2)	129(44.2)	
Total	4(1.4)	288(98.6)	292(100)	

***Fishers exact test**

4.4 Proportion of mortality among study participants

Overall 40.8% (119) of both controls and intervention died before the end of the neonatal period (as shown in figure 4). The overall mortality was 41.7% (68) among controls and 39.5% (51) of intervention (p=0.72, OR= 0.91; 95CI 0.57- 1.46)**.** Mortality among VLBW controls was 33.3% (23) while intervention group had 37.7 % (23) but this difference was not found to be statistically significant (p=0.6). Controls with HIE had mortality of 47.9% (45) while intervention group had 41.2% (28) (p=0.4 as shown in figure 5)

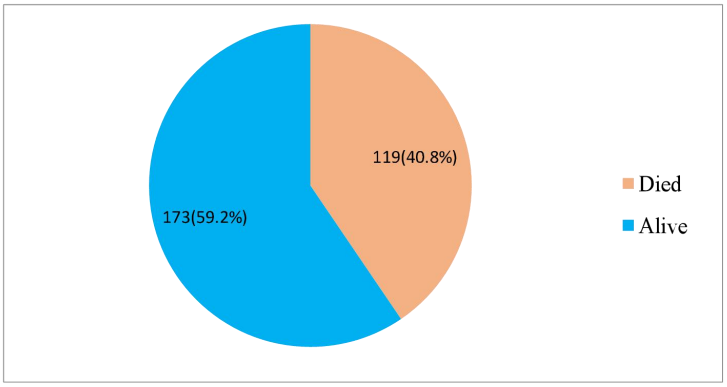


Figure 4: A pie chart showing the overall proportion of mortality among study participants

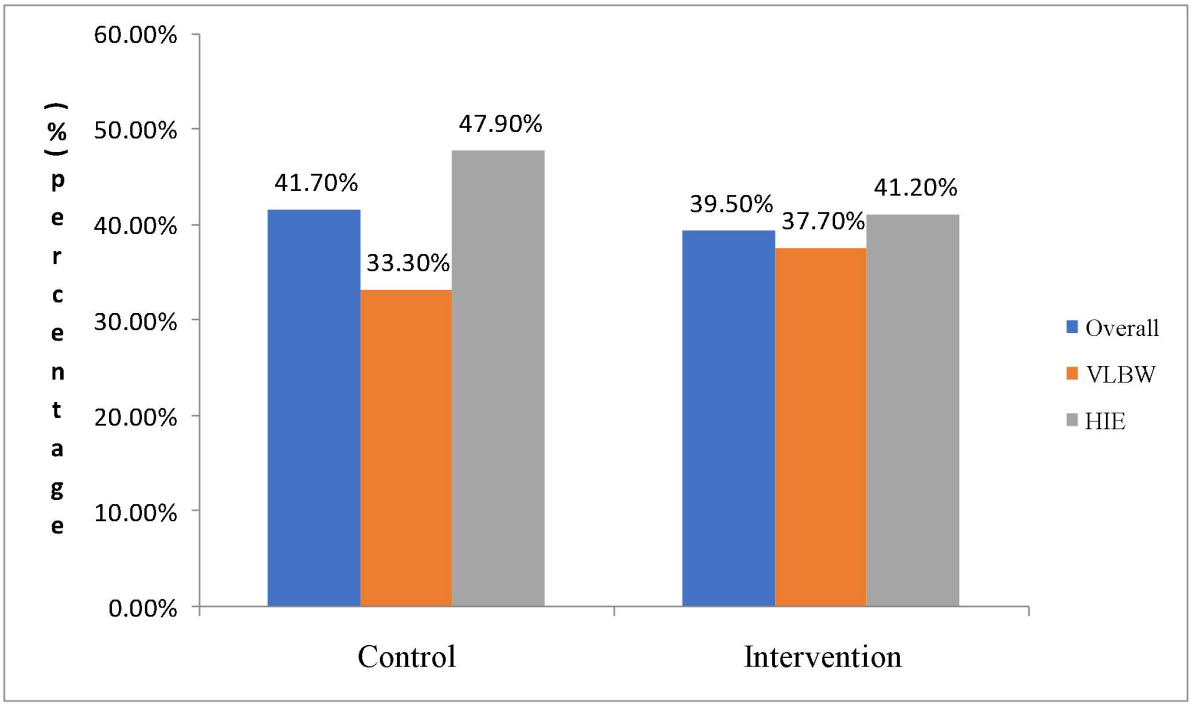


Figure 5: Bar chart showing proportion of mortality among the study participants

4.5 Proportion of study participants who regained weight before the study end point

Among the study participants' 33.1% of the controls and 43.45% of the intervention group regained birth weight before study end point. In neonates with VLBW, 58.0% of the controls regained birth weight while 60.7% of the intervention group regained birth weight. Of those with HIE, 14.9% of the control group and 27.9% of the intervention group regained their birth weight before study end point as shown in figure 6.

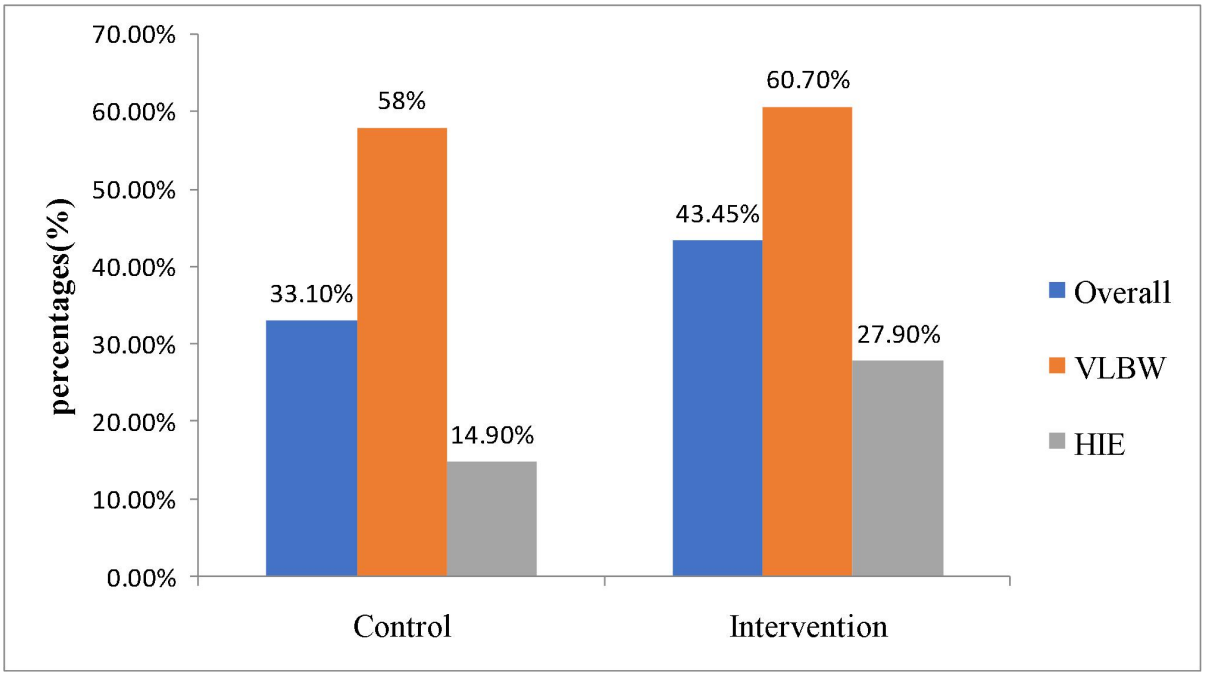


Figure 6: Histogram showing proportion of study participants who regained weight before study end point

4.6 The mean age of regaining birth weight among study participants

The mean time of regaining birth weight among control group was 11.26 ± 4.34SD days and 8.25 ± 2.96SD days among the intervention group (p=0.000). Neonates with VLBW regained birth weight at 12.18 ± 4.64SD Vs 8.81 ± 3.23SD days (p=0.000), while those with HIE regained birth weight at 8.64 ± 1.50SD Vs 7.16 ± 1.98SD days (p=0.025) in control and intervention groups respectively as shown in table 4.

Table 4: Showing the mean age of regaining birth weight among study participants

Mean age regained birth weight (days)	Control n=54	Intervention n=56	*P* value	95% CI
Overall	11.26 ± 4.34SD	8.25 ± 2.96SD	**0.000**	1.61 - 4.41
VLBW	12.18 ± 4.64SD	8.81 ± 3.23SD	**0.000**	1.54 – 5.20
HIE	8.64 ± 1.50SD	7.16 ± 1.98SD	0.025	0.2 – 2.77

4.7 Duration of hospital stay among study participants

The mean duration of hospital stay was 9.02±7.83SD days in the control group and 8.85± 7.12 SD days among the intervention group (p=0.85). The mean duration of hospital stay was slightly longer among neonates with VLBW, 12.84 ±9.48SD days in control group Vs 11.95 ± 8.04 SD days in the intervention group (*p*=0.57); than neonates with HIE who had mean stay of 6.4 ±4.3SDdays in the control group Vs 5.94 ±4.3SD days in the intervention group (*p*=0.49) as shown in Figure 7.

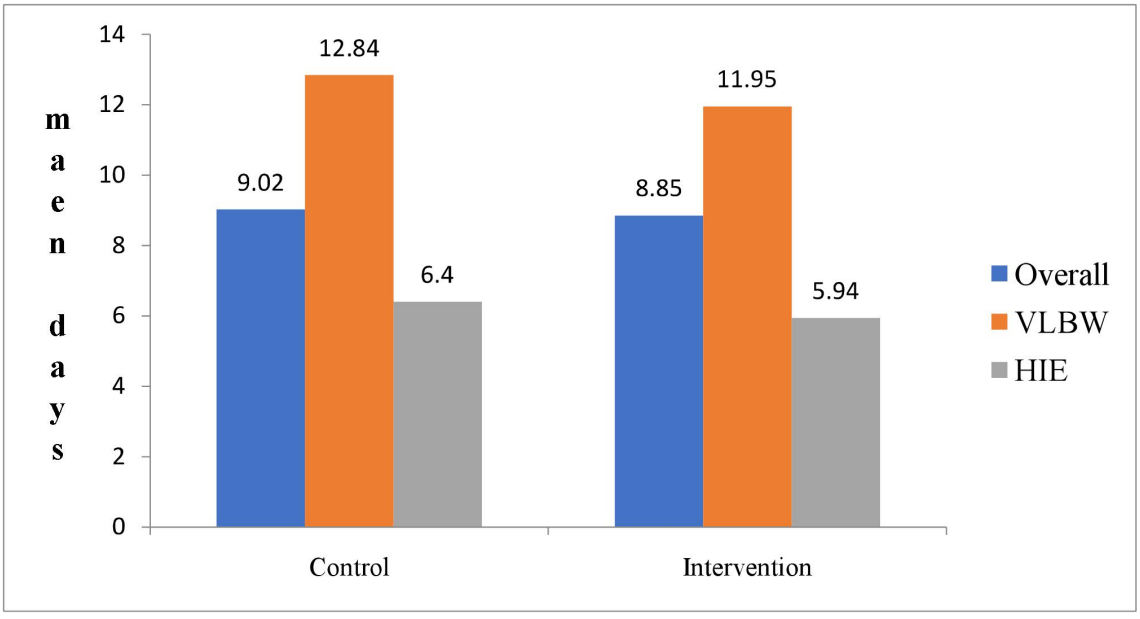


Figure 7: Histogram showing the duration of hospital stay among study participants

4.8 Factors associated with neonatal mortality among study participants

Table 5 shows bivariate analysis of selected independent factors in relation to occurrence of neonatal mortality. Most of the neonatal deaths, 72.3% occurred among neonates with mothers aged 20-34 years compared to <20 years and > 35 years who had mortality of 11.8% and 16 % respectively (p= 0.028).There was higher mortality in neonates with birth weight of ≤ 1200g than those with 1210 – 1500grams (50.9% vs. 23.3%; p= 0.001). Neonates with HIE score of ≥ 15 had higher mortality rate compared to those with < 15 (90.9% vs. 37.9%; p = 0.000)

Table 5: Factors associated with neonatal mortality among study participants

Category	Variable	Died		Total	*P* value
		Yes n=119	No n=173		
Sex	Male	63 (52.9)	93 (53.8)	156 (53.4)	
	Female	56 (47.1)	80 (46.2)	136(46.6)	0.89
Maternal age	<20years	14(11.8)	21(12.1)	35(12.0)	
	20 -34 years	86(72.3)	141(81.5)	227(77.7)	
	>34years	19(16.0)	11(4.4)	30(10.3)	**0.028**
Maternal education	No formal education	17(14.3)	16(9.2)	33(11.3)	
	Primary school	65(54.6)	101(58.4)	166(56.8)	
	Secondary school	34(28.6)	49(28.3)	83(28.4)	
	Higher education	3(2.5)	7(4.0)	10(3.4)	0.52*
Parity	Para 1	45 (37.8)	82(47.4)	127(43.5)	
	Para 2	30 (25.2)	45(26.0)	75(25.7)	
	≥para3	44 (37.0)	46(26.6)	90(30.8)	0.14
HIV	Positive	10 (8.4)	7(4.0)	17 (5.8)	
	Negative	109 (91.6)	166(96.0)	275(94.2)	0.12
PIH	Yes	10(8.4)	12(6.9)	22(7.5)	
	No	109(91.6)	161(93.1)	270(92.5)	0.64
Malaria	Yes	11(9.2)	9(5.2)	20(6.8)	
	No	108(90.8)	164(94.8)	272(93.2)	0.18
Anemia	Yes	16(13.4)	21 (12.1)	37 (12.7)	
	No	103 (86.6)	152(87.9)	103(86.6)	0.72
UTI	Yes	8(6.7)	4 (2.3)	12(4.1)	
	No	111(93.3)	169(97.7)	280 (95.8)	0.062*
Weight	≤1200g	29(50.9)	28(49.1)	57(19.5)	

	1201-1500g	17(23.3)	56(76.6)	73(24.9)	**0.001**
	≥ 2500g	73(45.3)	88(54.7)	162(55.5)	
GA	27-32	39(38.2)	63(61.8)	102(35.0)	
	33-36	7(25)	21(75)	28(9.6)	
	≥37	73(45)	89(55)	162(55.5)	0.123
HIE	11-14	53(37.9)	87(67.1)	140 (47.9)	
	≥15	20(90.9)	2(9.1)	22 (7.5)	**0.000**
	Not applicable	46(35.4)	84(64.6)	13 (45.5)	
Feeding category	Control	68(57.1)	95(54.9)	163(55.8)	
	Intervention	51(42.9)	78(45.1)	129(44.2)	0.71

***Fishers exact test**

4.9 Multivariable logistic regression for determinants of mortality among study participants

Neonates born with birth weight of ≤1200g had increased risk of dying than those with > 1210g (AOR = 2.6, 95%CI: 1.18-5.85). Also among neonates with perinatal asphyxia, HIE score of ≥ 15 increases risk of mortality by 18 fold (95% CI: 4.0 - 82.3), table 6.

Table 6: Multivariable logistic regression for determinants of mortality among study participants

Variable	Died n=119	Alive n= 173	Crude Odds ratio 95% CI	P value	Adjusted Odds ratio 95% CI	P value
Maternal age						
<20years	14(11.8)	21(12.1)	1			
20 -34 years	86(72.3)	141(81.5)	0.92(0.44-1.90)	0.81	0.93(0.26-3.36)	0.91
>34years	19(16.0)	11(4.4)	2.6 (0.95-7.07)	0.06	0.68(0.26-1.7)	0.42
Gestational age						
27-32	39(38.2)	63(61.8)	1.86(0.72-4.77)	0.2	1.46(0.52-4.08)	0.47
33-36	7(25.0)	21(75)	1			
≥37	73(45.0)	89(55.0)	2.46(0.99-6.11)	0.05	2.64(0.96-7.25)	0.06
Weight						
≤1200g	29(50.9)	28(49.1)	3.4(1.61-7.23)	**0.001**	2.6(1.18-5.85)	**0.018**
1201-1500g	17(23.3)	56(76.6)	1			
≥ 2500g	73(45.3)	88(54.7)	2.73(1.46-5.11)	**0.002**	NS	
UTI						
Yes	8(6.7)	4 (2.3)	3.05(0.9-10.35)	0.075*	2.38(0.62-9.10)	0.21*
No	111(93.3)	169(97.7)	1			
Malaria						
Yes	11(9.2)	9(5.2)	1.51(0.65-3.47)	0.34	2.1(0.82-5.13)	0.12
No	108(90.8)	164(94.8)	1			

HIV						
Yes	10(8.4)	12(6.9)	2.18(0.80-5.89)	0.13	2.2(0.75-6.43)	0.15
No	109(91.6)	161(93.1)	1			
Parity						0.51
Para 1	45 (37.8)	82(47.4)	0.57(0.33-1.0)	0.048	1.27(0.63-2.53)	
Para 2	30 (25.2)	45(26.0)	1			
≥3	44 (37.0)	46(26.6)	0.70(0.38-1.30)	0.24	1.94(0.95-3.94)	0.069
HIE						
11-14	53(37.9)	87(67.1)	0.9(0.55-1.48)	0.67		
≥15	20(90.9)	2(9.1)	16.42(3.69-73.06)	0.000*	18.12(4.0-82.3)	**0.000***
Not applicable	46(35.4)	84(64.6)	1			

***Fishers exact test**

CHAPTER FIVE

5.0 DISCUSSION

The aim of this study was to determine the effect of early feeding using mother's milk on the incidence of necrotizing enterocolitis compared to nil oral feeding amongst VLBW and critically ill neonates in regional hospitals in Dar es Salaam. The mean age for initiation of feeding was 45.34 ± 21.58SD hours among controls compared to 8.43 ± 3.02SD hours of intervention. Our findings revealed that the overall proportion of NEC was 1.4% among the study participants. The mortality rate among control group was 41.5% while intervention had mortality rate of 39.5%. A birth weight of ≤1200g and HIE score ≥15 were independent predictors of mortality among neonates with very low birth weight and perinatal asphyxia respectively.

5.1 Proportion of necrotizing enterocolitis (NEC)

The overall proportion of necrotizing enterocolitis in this study was 1.4%. Only 3(1.8%) of controls and 1(0.8%) of intervention had necrotizing enterocolitis. This finding is similar to studies by Nickzehad *et al* who observed two cases of NEC, one case each group among 170 neonates with VLBW (18) and Mcclure and Newll who observed 1 case of NEC in trophic fed neonates and 2 cases in the in those with no trophic feeding (41). However, other several studies showed wide variation on the proportion of necrotizing enterocolitis ranging from 6.2% to 18% (22–24,30). A much higher proportion of NEC had been reported in studies which involved preterm growth-restricted neonates with abnormal antenatal Doppler studies. But none of these studies found these differences in proportion of NEC to be statistically significant.

In this study, only 1 neonate with HIE from the delayed feeding group had NEC. This study didn't demonstrate the effects of feeding on NEC among neonates with HIE in both control and intervention groups. There is limited data on association between feeding and the incidence of necrotizing enterocolitis among neonates with HIE to support withholding feeds.

The inconsistency in proportion of NEC observed in VLBW between this study and some previous studies may be contributed by the following factors: firstly involvement of neonates with growth-restriction and AREDF in the umbilical artery (21–24) while this study included all VLBW. Neonates with IUGR and AREDF have a higher risk of NEC due to redistribution of blood to vital organs (brain development, cardiac and adrenal gland) with poor flow to the gut predisposing gut to hypoxic-ischemic injury. Secondly , neonates with extremely low birth weight were included in some of the studies (23,24) which further increase the risk of NEC as the incidence of NEC is inversely related to birth weight and gestational age (22,24). Thirdly, use of mixed feeding as infant formula increases the risk of NEC (16,17).

5.2 Neonatal mortality

The overall mortality rate observed in this study was 40.8% with no significant difference between control and intervention groups (41.5% Vs 39.5%). Mortality rate among neonates with VLBW was 33.3% in the control group compared to 37.7% of the intervention group. The mortality rate observed in this study was higher compared to that reported by Celik *et al* in Turkey and Tewari *et al* in India (19,21). Low neonatal mortality observed in Turkey and India compared to this study may be due to the fact that they were done in middle income countries with improved neonatal care compared to this study which was done in a resource limited country.

This study also found a birth weight of < 1200g to be an independent risk factor for mortality regardless of the timing of initiation of feeding which is similar to that reported by Tewari *et al* (21).

Mortality rate among neonates with HIE in this study was 47.9% in the control group compared to 41.2% of the intervention group. Severe HIE is an independent determinant of mortality irrespective of timing of feeding. There is limited data on effects of early feeding among neonates with HIE although perinatal asphyxia had been identified as a leading cause of neonatal mortality worldwide and poses feeding difficulties in neonatal units.

Although previous studies reported early provision of mother's milk decreases mortality and morbidity among VLBW neonates (15–17), this study did not demonstrate effect of feeding on reduction of mortality on both neonates with VLBW and HIE. A study with a larger sample size with higher power is required in order to determine this safety effect.

5.3 Duration of regaining birth weight

The intervention group significantly regained birth weight earlier than the controls; the mean age of regaining birth weight was 11.26 ± 4.34SD days in control group compared to 8.25 ± 2.9SD days among the intervention group. The mean duration of regaining birth weight among neonates with VLBW was 12.18 ± 4.64SD Vs 8.81 ± 3.23SD days in control and intervention groups respectively. Significant shorter time of regaining weight among the intervention than controls observed in this study was similar to that observed by Niknezhad *et al* and *Tewari etal* whereby VLBW preterm infants who received early feeding regained birth weight 7 days earlier than the delayed feeding group (18,21). Despite the use of TPN concurrent to enteral feeding, which may shorten the time of regaining birth weight, neonates from the two studies regained birth weight later than neonates in this study who received breast milk alone.

Contrary to this study, a randomized controlled trial by Abdelmaaboud *et al* among VLBW with IUGR found no significant difference in duration of regaining birth weight between the early and delayed fed neonates (24). The definition of early feeding varies between these studies whereby in the this study early feeding group started feeding within 24hours of life while Abdelmaaboud *et al* initiated feeding on the 3rd day of life. This may have contributed to reduced gut functional adaptation and excessive physiological weight loss hence prolonged duration of regaining birth weight in both groups.

In this study among the neonates with HIE, the intervention group regained birth weight earlier than the control group with the mean age of 7.16 ± 1.98 SD Vs 8.64 ± 1.50SD days respectively . Only 33.1% of neonates with HIE regained birth weight in this study, but they regained birth weight earlier than those with VLBW.

5.4 Duration of hospital stay

The mean duration of hospital stay among VLBW neonates was 12.84 ±9.48SD Vs 11.95 ± 8.04 SD days among controls and intervention groups respectively with no statistical significance. The mean duration of hospital stay observed in this study was shorter and comparable to that observed by Niknezhad *et al* and Romano *et al* (18,20). Although these two studies found a significant difference in duration of hospital stay, most studies have not illustrated a significant reduction in hospital stay among early and delayed feeding groups.

Neonates with HIE had a mean duration of hospital stay of 6.4 ±4.3SD days among controls and 5.94 ±4.3SD days in an intervention. Neonates with HIE in this study had shorter mean duration of hospital stay compared to that found by Chang *et al* and Thyagarajan *et al* whereby neonates with HIE who were on therapeutic hypothermia were receiving MEN (26,42) . Although therapeutic hypothermia had gut protective effects hence expected to have synergistic and better outcomes, but neonates had longer hospital stay than those from this study. This may be contributed by short duration of trophic feeding done in this study as some previous evidence indicated it improves feeding tolerance, rapid recovery and hence early discharge (29,30).

5.5 Feeding adverse events

The overall 11.3% of the participants had feeding adverse events whereby 11.7% occurred in the control group and 10.1% in the intervention group. Most of the feeding adverse events occurred after 72 hours of life. Aspiration was the most common encountered feeding adverse events in both the control (8.0%) and the intervention groups (6.2%) as shown in appendix 1 and 2.

5.6 Strength of the study

- Feeding was started very early within 24hours of life compared to several previous studies whereby the early feeding group started feeding 4 -5 days of life.
- There was a rapid but safe progressive feeding advancement of trophic feeding as per the recommended standard WHO feeding guideline.

- Historical controls were recruited and the variables of interest were properly documented which created a more comparable group.

5.7 Limitation

- A quasi-experimental design with historical control can lead to bias due to change in the study population over time.
- Neonates who had been referred to tertiary hospital were not followed to determine their outcomes. This might result to an underestimation of proportion of necrotizing enterocolitis and mortality.

CHAPTER SIX

6.0 CONCLUSION AND RECOMMENDATION

6.1 Conclusion

Early feeding using mother's milk via oral mucosal colostrum or minimal enteral nutrition was not associated with a higher risk of NEC or an increase in mortality in neonates with VLBW and HIE but this study was underpowered to measure these safety outcomes. However, neonates initiated on early feeding regained birth weight significantly earlier than those with delayed feeding. A birth weight of $\leq$ 1200g and HIE score of $\geq$ 15 were found to be independent predictors of mortality among neonates with VLBW and HIE respectively.

6.2 Recommendation

A randomized study with large sample size and high power is recommended to further confirm the safety of early provision of mother's milk via OMC/trophic among neonates with VLBW and HIE in our setting. However, early provision of breast milk among neonates with VLBW and HIE promotes early weight gain, hence health workers should encourage mothers on breast feeding to promote growth and minimize hospital stay.

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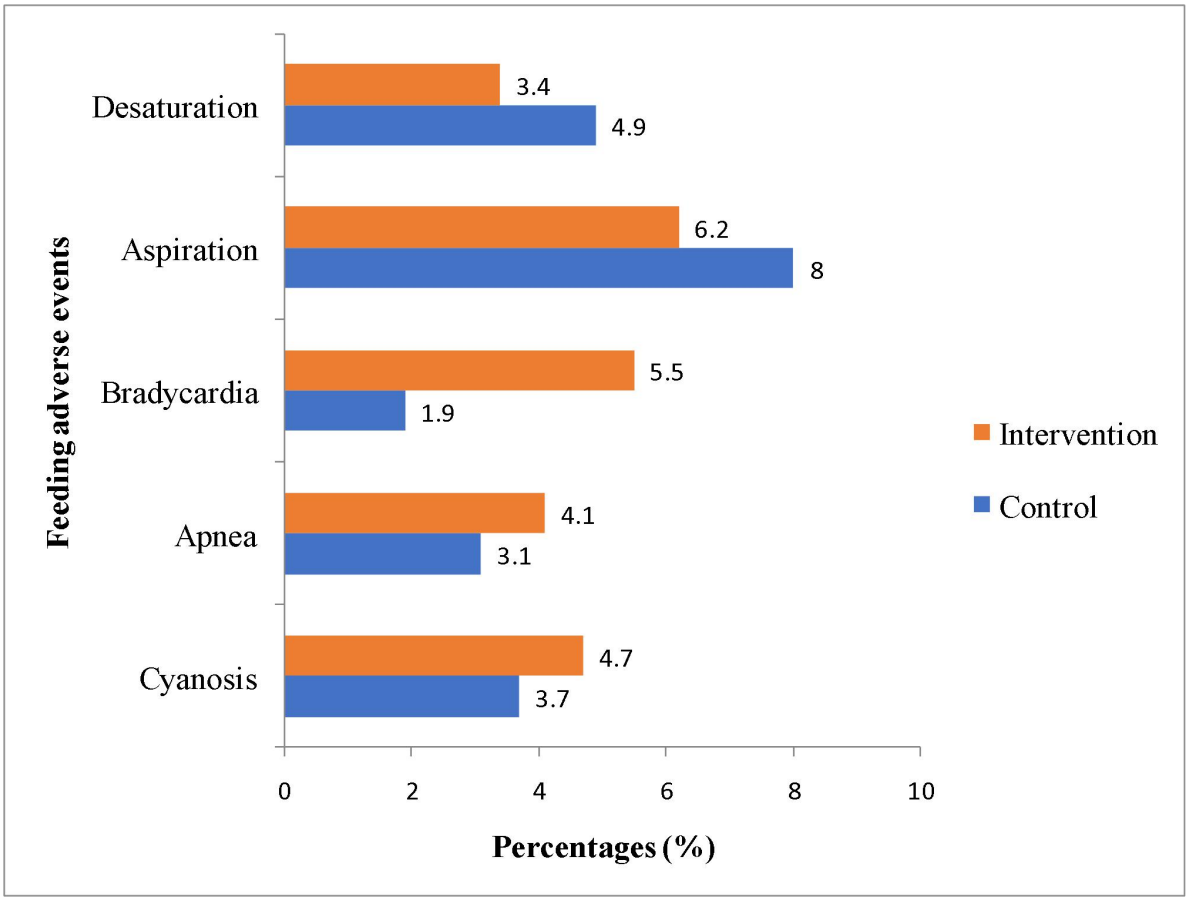
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APPENDICES

Appendices I: Feeding adverse events among study participants

Variable	Category	Control	Intervention	Total
Feeding adverse events	Yes	19 (11.7)	13(10.1)	32 (11.3)
	No	97(59.5)	111(86.0)	208(71.2)
	Not applicable	47 (28.8)	5(3.9)	51(17.5)
Interval between initiation of feeding adverse event	≤72hours	5 (26.3%)	4(30.8)	9(28.1%)
	>72hours	14(73.7%)	9(69.2%)	23(71.9%)

Appendices II: Histogram showing common feeding adverse events occurred



Appendices III: Consent Form (English Version)

EFFECTS OF EARLY FEEDS WITH MOTHERS' MILK AMONG NEONATES ADMITTED AT REGIONAL HOSPITALS IN DAR ES SALAAM

INTRODUCTION

My name is ……. I am a research assistant working on a study on effects of early enteral feeding using mother's milk among preterm neonates and critically ill neonates admitted in the three regional hospitals in Dar es Salaam. Your infant has been selected to participate in the study.

What does participation involve?

Your infant may be selected in one of two arms – the control arm where she/he will be fed no food until her symptoms subsides as indicated in the national treatment guidelines for management of such children or the intervention arm where she will be fed breast milk using a syringe or tube. In addition to feeding she will receive all other care such as measurement of body weight, temperature, respiratory rate and heart rate. Blood sample will be drawn for laboratory investigation to assess for presence of sepsis and other infections depending on your child's signs.

Confidentiality:

A unique study identification number will be used for each participant to ensure no information can be traced back to him or her. All information obtained from your infant will be handled in confidential manner and access will only be to the study investigators. All dissemination will be done in groups and no individual information will be shared.

Risk expected:

The study will not put your child at any extra risk than would be expected during the provision of care. Your child may experience minor pain during drawing of blood sample for laboratory investigations. The research team will follow standard procedures to ensure that this is

minimum and no other anticipated harm or danger which will arise by participating in this study.

Benefits:

By participating in this study your child will benefit from regular monitoring of feeding and vital signs, contribute to generating local evidence on benefits of early neonatal feeding using mother's milk in order to reduce neonatal mortality and improve quality of life. The acquired information will inform feeding guidelines used in neonatal care.

Compensation:

No compensation will be given to you or your child other than the benefits indicated above.

Your rights:

Your participation in this study is voluntary. If you so decide to allow your child to participate in the study, you may withdraw your child from the study at any time and this decision will not affect the standard of care given to your child during hospitalization. Information collected before withdrawing will continue to be used in the research.

Whom to contact:

If you have questions about this study, you can call the principal investigator: Dr Regina O Hyera (0767865531) during working hours. You can also contact the Director of Research and Publications, Muhimbili University of Health and Allied Sciences, Dr Bruno Sunguya, P.O.Box 65001, Dar es Salaam. Phone number: 2150302-6

CONSENT

I…….confirm that, I have read/or have had this form read to me and understood the contents of this form. My questions have been answered. I agree for my infant to participate in this study.

Name of mother ……

Signature of mother ……

Date ……/……/…… Signature of researcher/research assistant ……

Appendix IV: Consent Form (Kiswahili Version)

RIDHAA YA KUSHIRIKI KWENYE UTAFITI

UMUHIMU WA KUWALISHA MAPEMA MAZIWA YA MAMA WATOTO WACHANGA WENYE UZITO CHINI YA GRAMU 1500 NA WANAOUMWA WALIOLAZWA KATIKA HOSPITALI ZA MKOA WA DAR-ES-SALAAM

Utangulizi.

Naitwa….....,ni mwanafunzi wa udaktari bingwa wa watoto/ msaidizi wa katika huu utafiti huu. Ninafanya utafiti juu ya matokeo ya kuwahi kuwalisha maziwa ya mama watoto wachanga wenye uzito chini ya gramu 1500 na wanaoumwa waliolazwa katika hospitali za rufaa za mkoa huu wa Dar es salaam. Mtoto wako anaombwa kushiriki katika utafiti huu kwasababu chakula ni sehemu muhimu katika matunzo na uhai wa watoto wa changa.

Mtoto wako atakuwa anajitolea, uamuzi wako wa kuruhusu au kutoruhusu motto wako kushiriki katika utafiti huu hautakuwa na athari zozote kwenye huduma za matibabu ya motto wako wakati akiwa amelazwa. Kama kuna kitu chochote kuhusu huu utafiti ambacho hujakielewa unaweza kuuliza maswali wakati wowote wa utafiti.

Ushiriki una mambo yapi:

Mtoto wako atachunguzwa na kupimwa uzito, joto la mwili, kasi ya upumuaji na mapigo ya moyo wakati analazwa. Atatolewa damu kwa ajili ya uchunguzi kama anauambukizo kwenye damu mwanzoni mwa utafiti pia anaweza kutolewa wakati wowote kama ana vijidudu vya magonjwa kwenye damu atatibiwa. Ataanzishiwa kula kwa kutumia maziwa yako kadri utakavyoelekezwa na mhudumu wa afya na matibabu mengine ambayo yanatolewa kwa watoto waliolazwa kama antibiotiki ya msuli na kuongezewa maji yataendelea kulingana na mahitaji ya mtoto. Mtoto ataangaliwa kwa ukaribu na mhudumu wa afya na wewe mwenyewe kama utaona tatizo toa taarifa kwa mhudumu ili lishugulikiwe mapema.

Usiri:

Utambulisho wa motto utakuwa kwa namba ili kutunza usiri wa motto wako. Pia maelezo yeyote yatakayochukuliwa yatawekwa siri na kutunzwa na mtafiti. Taarifa za maandishi zihusuzo utafiti zitatunzwa kwenye kompyuta zenye ulinzi na rekodi, zilizopo kwenye makaratasi zitatunzwa kwenye makabati yanayofungwa

Taarifa za utafiti ikiwa ni pamoja na taarifa za motto wako zinaweza kutolewatu ikiwa serikali au wizara ya afya inazihitaji kwa matumizi ya ofisi ikiwa ni pamoja na kuboresha huduma za afya.

Athari zinazotarajiwa

Zaidi ya maumivu kiasi kidogo wakati wa kutolewa damu ya vipimo hakuna madhara yananayotarajiwa katika kushiriki utafiti huu. Ikiwa motto atapata tatizo unalohisi limetokana na utafiti huu usisite kuwasilia na na Dk. Regina Hyera (0767865531) au uongozi wa chuo kikuu cha afya na tiba shirikishi Muhimbili

Faida

Kushiriki katika utafiti huu unasaidia kuongeza uelewa wa kisayansi faida ya kuwalisha watoto wachanga maziwa ya mama ili kupunguza vifo vya watoto wachanga na kuboresha afya zao. Uelewa huo unaweza kusaidia katika kuandaa miongozo ya matunzo ya watoto wachanga pia kusaidia watumishi wa afya katika kuongeza ufanisi wa huduma za watoto wachanga

Haki yako.

Unahaki ya kukubali au kukataa motto wako kushiriki katika utafiti huu. Kama utaamua kusitiisha motto wako katika utafiti huu kwasababu yoyote ile, utasitisha ruhusa yako baada ya kuwasiliana na mtafiti/ mtafiti msaidizi. Taarifa zitazokusanywa kabla ya kusitishwa ruhusa zitatumika katika utafiti.

Mawasiliano.

Ikiwa una maswali yoyote kuhusu utafiti huu, wasiliana na mkurugenzi wa Tafiti chuo kikuu cha Afya na Sayansi shirikishi za tiba Muhimbili, Dr Joyce Masalu, P.O.Box 65001 Dar es Salaam.

Simu ya mezani: 2150302-6.

RIDHAA

Mimi……. Nathibitisha kuwa nimesoma/ nimesomewa maelezo katika fomu hii na kuyaelewa. Maswali yangu yamejibiwa. Nakubali motto wangu kushiriki katika utafiti huu.

Jina la mama ……

Sahihiya mama ……

Tarehe ……/……/……

Sahihi ya mtafiti/mtafiti msaidizi ……

Appendix V: **Case Report Form**

EFFECTS OF EARLY ENTERAL FEEDS WITH MOTHERS' MILK AMONG NEONATES ADMITTED AT REGIONAL HOSPITALS IN DAR ES SALAAM

S/N	QUESTION	RESPONSE
1	Study group	1. Control 2. Intervention
2	Patient identification number (ID)	
3	Name of hospital	
4	sex	1. Male 2. Female
5	Date of birth	……/……../……..
6	Time of birth	……. Hours
7	Date of admission	……/……./…….
8	Time of admission	……. Hours
9	Age during admission	…… Hours
10	Reason for admission	1. VLBW 2. HIE
11	Gestational age (using last normal menstruation)	……weeks
12	Gestational age (Ballard score)	……weeks
13	Apgar score (term neonate)	1st minute…… 5th minute……
14	HIE score (term neonate)	
15	Vital signs during admission	Temperature…… Pulse rate…… Respiratory rate…….. Oxygen saturation ……
16	Maternal age	……. Years

17	Maternal education	1.No formal education 2. primary education 3.Secondary education 4.Higher education
18	Parity	Para ……
19	Any maternal morbidity	1. Yes 2. No
20	Morbidities	1. HIV 2. Hypertension 3. Malaria 4. Anemia 5. Diabetes mellitus 6. Syphilis 7. Urinary tract infection 8. Others mention ……..
21	Birth weight (From RCH card)	……. Grams
22	Weight during admission	…… Grams
23	Started feeding **(If No Q34)**	1. Yes 2. No
24	Date and time started feeding	Date ……/……./……. Time ……..Hours
25	Feeding method during initiation of breast milk	1. NGT 2. Cup 3. NGT and cup 4. Cup and breast feeding 5. OMC
26	Feeding method during discharge	1. NGT 2. Cup 3. Cup and breast feeding

		4. Breast feeding only
27	If Breast feeding only	Date breastfeeding only ……/……/…..… Age breastfeeding only …….. days
28	Regained birth weight	1. Yes 2. No
29	**If yes Q28**	Date ……..
30	Minimum weight attained	…….. Grams
31	Maximum weight loss	…….. Grams ……. Percentage (%)
32	Any interrupted feeding	1. Yes 2. No
33	If yes, type of interruption	1. Stop feeding 2. Reduce amount of milk
34	Reason for interruption	1. Feeding intolerance 2. Feeding adverse event 3.Supected NEC
35	Signs of necrotizing enterocolitis (NEC)	1. Yes 2. No
36	If yes Q34, X ray findings	Hospital radiologist……. Other radiologist…….....
37	Confirmed NEC	1.Yes 2. No
38	Date during study end point	……./……./……
39	Age during study end point	……. Days
40	Reason for study end point	1. Discharge 2. Age > 28days of life 3. Death 4. Referral

		5. Discharge against medical advise
Feeding adverse events		
41	Date feeding adverse occurred	……./……/……. Time …….. Hours
42	Interval between initiation of feeding and feeding adverse event	…….days and/or …….hours
43	Age of neonate during feeding adverse event	…….. days
44	Type of events occurred	1. Aspiration/chocking 2. Cyanosis 3. Apnea 4. Tachypnoea 5.Bradycardia 6. desaturation
45	Management received after feeding event	
46	Outcome	
47	If death interval between adverse event and death	

Appendix VI: Form ya Kurekodi Taarifa za Mtoto

S/N	Swali	Jibu
1	Kundi la utafiti	1. Control 2. Intervention
2	Nambari ya utambulisho	
3	Hospital	
4	Jinsia ya mtoto	1. Mwanaume 2.Mwanamke
5	Tarehe ya kuzaliwa	……/……/…….
6	Muda wa kuzaliwa	…….. (masaa 24)
7	Tarehe ya kulazwa	……/……../……
8	Muda wa kulazwa	……
9	Umri wa mtoto wakati wa kulazwa	Saa……..
10	Sababu ya kulazwa	1. VLBW (1000-1500g) 2. HIE(>10)
11	Umri wa mimba wakati wa kujifungua (LNMP)	Wiki …….
12	Umri wa mimba wakati wa kujifungua (ballard score)	Wiki ……
13	Apgar score (aliyetimiza miezi tisa)	Dakika 1….. Dakika 5……
14	HIE score (aliyetimiza miezi tisa)	
15	Vital signs	Joto …….. C, kasi ya upumuaji ……. Mapigo ya moyo……. Kiwango cha oxygen…….
16	Umri wa mama	Miaka ……
17	Elimu ya mama	1. Hajasoma kabisa

		2. Elimu ya msingi 3. sekondari 4. Elimu ya juu
18	Amezaa mara ngapi	
19	Mama ana tatizo lolote la kiafya	1. Ndiyo 2. Hapana
20	Matatizo ya kiafya ya mama	1. VVU 2. Shinikizo la damu 3. Malaria 4. Upungufu wa damu 5. kisukari 6. Kaswende 7. Maambukizi njia ya mkojo 8. Mengineyo …….
21	Uzito aliozaliwa nao	…… Grams
22	Uzito wakati wa kulazwa	……. Grams
23	Mtoto ameanza kula	1.Ndiyo 2. Ndiyo
24	Tarehe na muda wa kuanza kula	Tarehe ……/……./……. Muda ……
25	Njia ya kulisha mtoto wakati anaanza kula	1.Mrija wa chakula 2. Kikombe 3. Mrija na kikombe 4. kikombe na kunyonya 5. OMC
26	Njia ya kula wakati wa kusitisha kukusanya taarifa	1.Mrija wa chakula 2. Kikombe 3. Mrija na kikombe 4.kikombe na kunyonya

		5. Kunyonya tu
27	Mtoto amewahi kunyonya tu ?	1. Ndiyo 2. Hapana
28	Mtoto amewahi fikia uzito aliozaliwa nao?	1. Ndiyo 2. Hapana
29	Kama **ndiyo swali 28**	Tarehe……/……/…….
30	Uzito mdogo aliowahi fikia mtoto	…….. grams
31	Uzito aliopoteza mtoto	…….grams … ……. asilimia (%)
32	Mpangilio wa kulisha mtoto umewahi vurugika?	1.Ndiyo 2. Hapana
33	Kama ndiyo **swali 31**	1. Kuacha kulisha 2. Kupunguza kiwango cha maziwa
34	Sababu ya kuvuruga mpangilio wa chakula	1.Kushindwa kustahimili chakula 2.Madhara yatokanayo na ulishaji 3. Alidhaniwa kuwa na NEC
35	Mtoto ana dalili za NEC?	1. Ndiyo 2. Hapana
36	Majibu ya X ray	Mtaalamu wa hospitali …… Mtaalamu mwingine ……
37	Amethibitishwa kuwa na NEC	1. Ndiyo 2. Hapaana
38	Tarehe ya kusitisha kukusanya taarifa	……/……/…….
39	Umri wa mtoto wakati wa kusitsha kukusanya taarifa	Siku …….
40	Sababu ya kusitisha kukusanya taarifa	1. Ameruhusiwa 2. Umri zaidi ya siku 28

		3. Amefariki 5. Amepewa rufaa 6. Ameondoka bila ridhaa ya daktari
Madhara yatokanayo na ulishaji		
41	Tarehe ambayo madhara yalitokea	……/……../……
42	Muda toka aanze kula hadi apate madhara	Saa ……..
43	Umri wa mtoto wakati amepata madhara	Siku ……..
44	Aina ya madhara yaliyotokea	1. Kupaliwa 2. Rangi ya bluu 3. kuacha kupumua 4.Mapigo ya moyo kupanda 5.Mapigo ya moyo kushuka 6.kiwango cha oxygen kushuka
45	Tiba aliyopata mtoto	
46	Matokea wakati wa kusitisha taarifa	
47	Kama amefariki muda toka alipopata madhara hadi kifo	Siku ……. Saa…….

Appendix VII: Feeding Chart

Hospital …….. Patients ID ……..

Birth weight……grams Date when feeding started …../……/……

Time…….. Hours

Date	**weight**	**Volume of fluid**	**OMC**	**Volume of milk(mls)**											

Appendix VIII: Monitoring Charts

HOSPITAL…… SERIAL NUMBER ……

FIRST DAY OF LIFE

Feeding frequency	BEFORE FEEDING					10MINUTES AFTER FEEDING							
1	RR	PR	SPO2	Apnea	cyanosis	RR	PR	SPO2	Apnea	cyanosis	chocking	aspiration	vomiting
2													
3													
4													
5													
6													
7													
8													
10													
11													
12													

Any event occurs between feeding (> 10minutes before another feeding)
Aspiration …… Desaturation/decrease in SPO2 ……Apnea …… Vomitting ……..
Cyanosis…….. Chocking ……
SECOND DAY OF LIFE

Feeding frequency	BEFORE FEEDING					10MINUTES AFTER FEEDING							
1	RR	PR	SPO2	Apnea	cyanosis	RR	PR	SPO2	Apnea	cyanosis	chocking	aspiration	vomitting
2													
3													
4													
5													
6													
7													
8													
9													
10													
11													
12													

Any event occurs between feeding (> 10minutes before another feeding)

Aspiration …… Desaturation/decrease in SPO2 ……

Apnea …… Vomitting ……..

Cyanosis……..

Chocking ……

THIRD DAY OF LIFE

Feeding frequency	BEFORE FEEDING					10MINUTES AFTER FEEDING							
1	RR	PR	SPO2	Apnea	cyanosis	RR	PR	SPO2	Apnea	cyanosis	chocking	aspiration	vomitting
2													
3													
4													
5													
6													
7													
8													
9													
10													
11													
12													

Any event occurs between feeding (> 10minutes before another feeding)

Aspiration …… Desaturation/decrease in SPO2 ……

Apnea …… Vomitting ……..

Cyanosis…….. Chocking ……

FOURTH DAY OF LIFE

Feeding frequency	BEFORE FEEDING					10MINUTES AFTER FEEDING							
1	RR	PR	SPO2	Apnea	cyanosis	RR	PR	SPO2	Apnea	cyanosis	chocking	aspiration	vomitting
2													
3													
4													
5													
6													
7													
8													
9													
10													
11													
12													

Any event occurs between feeding (> 10minutes before another feeding)

Aspiration …… Desaturation/decrease in SPO2 ……

Apnea …… Vomitting ……..Cyanosis…….. Chocking

FIFTH DAY OF LIFE

Feeding frequency	BEFORE FEEDING					10MINUTES AFTER FEEDING							
1	RR	PR	SPO2	Apnea	cyanosis	RR	PR	SPO2	Apnea	cyanosis	chocking	aspiration	vomitting
2													
3													
4													
5													
6													
7													
8													
9													
10													
11													
12													

Any event occurs between feeding (> 10minutes before another feeding)

Aspiration …… Desaturation/decrease in SPO2 ……

Apnea …… Vomitting ……..

Cyanosis…….. Chocking ……

Appendix IX: Adverse Events Report Form

EFFECTS OF EARLY ENTERAL FEEDS WITH MOTHERS' MILK AMONG VERY LOW BIRTH WEIGHT AND CRITICALLY ILL NEONATES ADMITTED AT REGIONAL HOSPITALS IN DAR ES SALAAM

<table>
<tr><td>Phase of study</td><td colspan="2">Serial NO</td><td>Patient ID</td></tr>
<tr><td>Date enrolled</td><td>Hospital</td><td>Sex</td><td>DOB</td></tr>
<tr><td colspan="2">Date feeding started</td><td colspan="2">Age feeding started</td></tr>
<tr><td colspan="4">Reason for admission:</td></tr>
<tr><td colspan="2">Date adverse events occurred</td><td colspan="2">Age of neonate</td></tr>
<tr><td colspan="4">Interval between initiation of feeding and occurrence of adverse event</td></tr>
<tr><td rowspan="3">Events occurred</td><td>NEC ( )</td><td>Cyanosis ( )</td><td>Apnea ( )</td></tr>
<tr><td>Aspiration ( )</td><td>Desaturation ( )</td><td>Tachycardia ( )</td></tr>
<tr><td>Bradycardia ( )</td><td colspan="2">Tachypnea ( )</td></tr>
<tr><td>Brief description of participants condition before adverse events</td><td colspan="3"></td></tr>
<tr><td>Brief description of the nature of the adverse event</td><td colspan="3"></td></tr>
</table>

Investigations done if any	X Ray	CBC	
Intervention provided after adverse feeding event	Suction ( )	Surgery ( )	Referral ( )
	Reduce feeding volume ( )	Antibiotics ( )	
	Stop feeding ( )	Oxygen therapy ( )	
Does the event related to early feeding?	Yes ()	No (): Feeding started after 24 hours	
Outcome after feeding event	Alive ( )	Died ( )	Referral
Interval between feeding adverse events and death			

Appendix X: Ballard score

Neuromuscular Maturity

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

Physical Maturity

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

Maturity Rating

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

Appendix XI: Thompson score

Table-1: Thompson Score.

Sign	0	1	2	3
Tone	Normal	Hypertonia	Hypotonia	Flaccid
LOC	Normal	Hyperalert, Stare	Lethargic	Comatose
Fits	None	< 3 Per Day	> 2 Per Day	
Posture	Normal	Fisting, Cycling	Strong Distal Flexion	Decerebrate
Moro	Normal	Partial	Absent	
Grasp	Normal	Poor	Absent	
Suck	Normal	Poor	Absent ± Bites	
Respiration	Normal	Hyperventilation	Brief Apnea	IPPV (Apnea)
Fontanel	Normal	Full, Not Tense	Tense	

Maximum Score = 22, Mild HIE: 1-10, Moderate HIE: 11-14, Severe HIE: 15.
LOC: Level of consciousness.

Appendix XII: Ethical Clearance

MUHIMBILI UNIVERSITY OF HEALTH AND ALLIED SCIENCES
OFFICE OF THE DIRECTOR OF POSTGRADUATE STUDIES

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Ref. No. DA.287/298/01A/

29th August, 2018

Dr. Regina O. Hyera
MMed. Paediatrics and Child Health
MUHAS.

RE: APPROVAL OF ETHICAL CLEARANCE FOR A STUDY TITLED: "EFFECTS OF EARLY ENTERAL FEEDS WITH MOTHER'S MILK AMONG PRETERM VERY LOW BIRTH WEIGHT AND CRITICALLY ILL NEONATES ADMITTED AT REGIONAL HOSPITALS IN DAR ES SALAAM"

Reference is made to the above heading.

I am pleased to inform you that, the Chairman has, on behalf of the Senate, approved ethical clearance for the above-mentioned study. Hence you may proceed with the planned study.

The ethical clearance is valid for one year only, from 27th August, 2018 to 26th August 2019. In case you do not complete data analysis and dissertation report writing by 26th August, 2019, you will have to apply for renewal of ethical clearance prior to the expiry date.

Dr. Emmanuel Balandya
ACTING: DIRECTOR OF POSTGRADUATE STUDIES

cc: Director of Research and Publications
cc: Dean, School of Medicine