COLLEGE OF MEDICINE

Association of Neonatal Hypothermia with Morbidity and Mortality in a Tertiary Hospital in Malawi

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(MBBS)

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DECLARATION

I, **Dr Frank Phoya,** declare that the contents of this thesis/dissertation constitutes my original work and has never been submitted to the University of Malawi or any other university.

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ABSTRACT

Background: Neonatal hypothermia is a major risk factor for morbidity and mortality in the first 28 days of life. Studies conducted, in high resource setting have shown the impact of hyperthermia on morbidity and mortality in the first 28 days of life, which has lead to better implementation of prevent measures. In sub-Saharan Africa, very limited data on the effect of hyperthermia on morbidity and mortality is available. Due to lack of data, this has led to poorly implemented interventions and slow reduction in the neonatal mortality rate. This study aimed to document the level of neonatal morbidity and mortality, associated with neonatal hypothermia. It determined whether hypothermia at 5 minutes, on admission to the neonatal unit (NU), or at 24 hours, had the highest association with morbidity and mortality.

Methods: This prospective observational study which was conducted at Queen Elizabeth Central Hospital, Blantyre Malawi recruited neonates with a birth weight greater than 1000 grams. Temperatures were recorded at birth, on admission and 4 hourly thereafter. Clinical course and outcome were reviewed. Data were analysed using Stata v.15 and $p < 0.05$ was considered statistically significant.

Results: Between August 2018 to March 2019, 120 neonates were enrolled, of which 112 had complete data and were included in the data analysis. Hypothermia at 5 minutes after birth was noted in 74% (83), 77% (86) on admission to the NU and 38% (24/63) at 24 hours. Neonates who had hypothermia 5 minutes after birth were more likely to have hypothermia on admission to the NU compared to normothermic subjects ($p<0.01$). Hypothermia on admission to the NU was significantly associated with mortality (100% v.72%, $p=0.02$) but not hypothermia at 5 minutes nor at 24 hours. After adjusting for potential confounders, the odds ratio of Apgar scores <6 at 1 minute for mortality was 5.66 (95% CI 1.55-20.70) for neonates with hypothermia compared to normothermia, and of hypothermia at 5 minutes for hypothermia on admission to NU was 13.31 (95% CI 4.17-42.54

Conclusion: This study highlights the large proportion of hospitalized neonates who are hypothermic on admission and the association between neonatal hypothermia and poor outcome in terms of morbidity and mortality. Our findings suggest that a strong predictor of mortality is neonatal hypothermia on admission to the NU, and that early intervention in the immediate period after delivery could decrease the incidence of hypothermia and reduce associated morbidity and mortality.

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ABBREVIATIONS

CI	Confidence Interval
COMREC	College of Medicine Research Ethics Committee
CPAP	Continuous Positive Airway Pressure
DHS	Demographic and Health Survey
ENAP	Every Newborn Action Plan
IVH	Intraventricular Hemorrhage
KMC	Kangaroo Mother Care
MDG	Millennium Development Goal
NEC	Necrotising Enterocolitis
NMR	Neonatal Mortality Rate
NICU	Neonatal Intensive Care Unit (able to intubate and ventilate**)**
NU	Neonatal Unit (No intubation and ventilation)
QECH	Queen Elizabeth Central Hospital
RDS	Respiratory Distress Syndrome
OR	Odds Ratio
UNICEF	United Nations International Children's Emergency Fund
WHO	Word Health Organization

CHAPTER 1: INTRODUCTION

1.1 Introduction

Every year, 130 million babies are born globally and 2.7 million die in the first 4 weeks of life [1]. Most of neonatal deaths (75%) occur in the first week of life, the highest risk of death is on the first day of life [2].

Worldwide neonatal mortality rate has fallen by 47% between 1990 and 2015 from 36 to 19 deaths per 1,000 live births. During the same period, the number of newborn babies who died within the first 28 days of life declined from 5.1 million to 2.7 [2]. However, the decline in neonatal mortality in 1990–2015 has been slower than that of post-neonatal under-five mortality (1-59 months). Neonatal mortality was at 47 %, compared with under five mortality at 58 % globally. This slow pattern applies to most low and middle-income countries. Neonatal deaths contribute 40% of all the deaths in children less than 5 years of age hence reducing neonatal deaths is an important target for the eventual reduction of childhood deaths overall [3].

The neonatal mortality rate is widely used as an indicator of public health, quality of health services, distribution of wealth and the general standard of living in a society. As many as 99% of the 2.7 million neonatal deaths that occur each year take place in the poorest countries of the world making neonatal health one of the most striking examples of health inequality [4]. The largest number of neonatal deaths occurs in South East Asia but this region has seen a dramatic drop in neonatal deaths as a result of several initiatives aimed at improving newborn health [2]. The actual number of neonatal deaths has remained constant in Africa, especially in the Sub-Saharan region accounting for almost 35% of underfive deaths in the region. Most of the countries (80%) with the highest neonatal mortality rates are in sub-Saharan Africa [2]. The neonatal mortality rate for high income countries is 3 per 1000 live births whereas in low-income and middle income countries it is estimated to be 26 per 1,000 live births. In sub-saharan Africa it's at 31 per 1000 live births [2].

In keeping with the global trend, Malawi has also shown reduction in under five mortality (it achieved the Millennium Development Goal MDG number 4, which was to reduce by two-thirds under five mortality, between 1990 and 2015) but the neonatal mortality has still remained high. In 2013 the WHO estimated that the neonatal mortality rate was 44.2 per 1000 live births. Currently the neonatal mortality is at 27 per a 1000 live births [5]. In light of this slow reduction in neonatal mortality rate (NMR), Malawi developed the "Newborn Action plan" from the Every Newborn Action Plan (ENAP), which was launched at the World Health Assembly in June 2014. This plan puts in place strategies to accelerate the reduction of preventable neonatal deaths and stillbirths in Malawi. Its goal is to reduce neonatal mortality from the present 27 per 1,000 live births to 23 by 2020, and 15 per 1,000 live births by 2035, with the ultimate goal of ending all preventable newborn deaths, including stillbirths.

Global estimates for the direct causes of neonatal deaths were prematurity (26%), severe infections (36%), complications of asphyxia (23%) and deaths related to congenital abnormalities (7%) [4]. Recently the global estimate for direct causes of neonatal deaths are preterm birth complications (35%), intrapartum related complications (24%), and sepsis (15%) [2].

Even though hypothermia is known to increase the risk of morbidity during the neonatal period thus leading to increase in mortality it has not be listed as one of the direct causes of death. However, it has been shown to be one of the risk factors for neonatal sepsis, intraventricular hemorrhage (IVH), necrotising enterocolitis (NEC), and has also be shown to increase the neonatal mortality rate [6]. In 2007 Word Health Organisation (WHO) recognised the importance of thermal care and came up with a practical guide for clinicians to follow. The guide, "Thermal Protection Of the Newborn", outlines ten steps that help to keep the neonate normothermic. The first step emphasises the need to have a warm delivery room, as the neonate loses a lot of body heat once delivered due to the difference in intrauterine and environmental temperature. The second highlights the importance of drying the baby immediately after birth, which helps remove the moisture that increases the evaporation of heat from the body. The third shows that putting the baby skin to skin with the mother not only helps increase bonding of baby and mother but it is the best method to keep the baby warm. The fourth encourages immediate breastfeeding (within the first hour after delivery), as this gives the baby the calories it needs to generate heat (neonates have a small amount of brown fat which is used to generate heat). The fifth point states that bathing and weighing the baby can be postponed as these are situations which leave the baby exposed and at increased risk of heat loss. The sixth point highlights the importance of appropriate clothing; the baby should be wrapped in a warm cloth and should have a hat. The seventh point re-emphasised that mother and baby should be kept together (rooming in), as this helps the baby keep warm and the baby is able to feed on demand. The eighth also highlights warm transportation as an important aspect of keeping the warm chain, as babies can lose lots of heat during transfer from delivery room to the neonatal intensive care unit (NICU). The ninth point states all resuscitations should be carried out in a warm environment (This is very important as babies who are born with asphyxia are not able to produce heat efficiently). The tenth point emphasises that all health care providers who are involved in care of the new born should be trained and aware of the nine principles used to maintain the warm chain. The ten steps highlight the standard of care which should be followed in NUs [6].

Hypothermia has been classified into 3 categories by the WHO (One) cold stress or mild hypothermia: 36.0 to 36.4 °C (96.8 to 97.5° F); (Two) moderate hypothermia: 32.0 to 35.9 °C (89.6 to 96.6° F); and (Three) severe hypothermia: below 32 °C (<89.6° F). Some studies have shown association between hypothermia and morbidity and mortality. A prospective cohort study done in Brazil by de Almeida *et* al. [7] which included 1764 inborn neonates between 22-33 weeks without malformations was looking at intervention practices associated with hypothermia at 5 minutes after birth and at NICU admission and to determine whether hypothermia at NICU admission is associated with early neonatal death in preterm infants. The study showed that hypothermia at five minutes after birth and at NICU admission was noted in 44% and 51% of neonates, respectively. After adjusting for confounders, practices associated with hypothermia at five minutes after birth included delivery room temperature <25°C, and maternal temperature at delivery <36.0°C. Hypothermia at NICU admission increased the chance of early neonatal death by 1.64-fold. Another study done by Miller *et al.* [8] looking at hypothermia in very low birth weight infants showed the distribution of hypothermia and associated risk factors and outcomes. The study enrolled 8,782 neonates with a mean birth weight and gestation age of 1072-278 g and 28.4-2.8 weeks, respectively. The mean admission temperature was 36.3 °C with a range of 26.1 to 39.6 °C; 30.5% were mildly hypothermic, 25.6% were moderately hypothermic, 0.1% were severely hypothermic, 43.0% were normothermic and 0.8% were noted to have a temperature 38.0 °C. During the study the incidence of hypothermia was greatest and the mean admission temperature lowest with decreasing gestational age and birth weight. In terms of risk factors, black (*P*=0.0001), Hispanic (*P*=0.0025) and other/unknown (*P*=0.04) races were associated with hypothermia, as were maternal hypertension, Cesarean section and low 1- and 5-minutes Apgar scores (*P*<0.0001). Antenatal steroid use (*P*<0.001), PROM (*P*<0.001), spontaneous labor (*P*<0.001), multiple births (*P*=0.006) and uterine infection (*P*<0.001) were associated with normothermia. There were no associations found with Asian race, maternal age, gender, prenatal care or maternal infection. Similar risk factors were seen for cold stress. In terms of the outcomes, no association between mild (cold stress) hypothermia and any of the morbidities (NEC, early-onset sepsis, late-onset sepsis or IVH) was found. Moderate hypothermia was associated with higher odds of IVH (odds ratio 1.3, 95% confidence limit 1.1 to 1.6) and death (odds ratio 1.5, 95% confidence limit 1.3 to 1.9). Severe hypothermia, although seen in only nine infants, was also associated with higher odds of death (odds ratio 5.6, 95% confidence limit 1.1 to 28.1). In low resource settings, a high incidence of hypothermia has been documented in hospitals immediately following birth; studies conducted in Zambia and Zimbabwe in the late 1990s to 2000s identified hypothermia in 44-51% of sick neonates On admission to the neonatal unit [9,10]. In addition, a recent audit done in Chatinkha nursey (Neonatal unit [NU]) at Queen Elizabeth central hospital (QECH), Malawi from January to December 2016 showed that out of the 2,975 files audited 41% of the neonates were admitted hypothermic and the highest mortality was in the neonates admitted with a temperature less than 32^0C (unpublished data).

1.2 Normal Care in NU

When we looked at the care offered at QECH, neonatal unit, neonates in the delivery room are placed under a radiant warmer before transfer to the NU or during resuscitation. Neonates are transferred wrapped in a cotton cloth in room air and no incubators are available for transfers. In the NU warmth is provided by radiant warmers and hot cots but these are usually few in number or not functional. No incubators are available in the NU.

Other care which is delivered to neonates includes: feeding, intravenous fluids, parenteral antibiotics, oxygen and continuous positive airway pressure (CPAP). There is no access to more sophisticated interventions such as surfactant therapy and mechanical ventilation. Kangaroo Mother Care (KMC) is initiated after achieving stabilisation, or intermittent KMC is done if the baby is still considered high risk.

1.3 Rationale for the Research Project

The above studies do shed some light on the effect of hypothermia on neonates and provide evidence of the need to prevent hypothermia as it contributes to a significant amount of morbidity and mortality. However, more recent data on hypothermia in neonatal units (NUs) in sub-Saharan Africa are lacking. Furthermore, few studies have evaluated whether hypothermia after birth, or on admission to the NU, or later, has the most impact on neonatal outcomes.

1.4 Research Question

The main aim was to identify the risk factors for the development of hypothermia in neonates with a gestational age above 28 weeks (birth weight ≥1000g), and the association of hypothermia with morbidity and mortality at QECH.

CHAPTER 2: OBJECTIVES

2.1 Primary Objectives

1. To identify the risk factors for the development of hypothermia in neonates with a gestational age above 28 weeks or birth weight ≥1000g born at QECH in the first 24 hours of life.
2. Primary endpoints were the neonatal hypothermia at 5 minutes after birth, on admission to NU, and at day 1 of life.

2.2 Secondary Objectives

1. To find the association of hypothermia in the first day of life with subsequent morbidity and mortality in the first 28 days of life.
2. Secondary endpoints were the in-hospital morbidity (respiratory distress syndrome (RDS), necrotising enterocolitis (NEC), intraventricular hemorrhage (IVH) and sepsis, (clinically suspected and culture/imaging-proven), time to stabilisation (duration of hospital stay, time to discharge, weight gain, normal vital signs, respiratory rate 40-60/min, no apnoea, no need for CPAP, oxygen saturation on room air >90%, heart rate 80-160/min, axillary temperature 36-37.4°C, no need for IV fluids and normal glucose levels for at least 24 hours), in-hospital mortality, and/or up to 28-days of life.

CHAPTER 3: METHODOLOGY

3.1 Type of Research Study

This was a prospective observational study in which study participants were followed up from birth to 28 days of life, death or discharge (depending on which came first)

3.2 Study Place

This study was conducted at QECH, Blantyre Malawi, NU (CHATINKHA nursery) which is a government funded tertiary level referral hospital serving the southern region of Malawi.

3.3 Study Population

Inclusion criteria

All neonates with a gestational age of ≥28 weeks, or birth weight of ≥1000g.

Exclusion criteria

Neonates with congenital abnormalities were excluded.

3.4 Study Period

The study was conducted between August 2018 to March 2019.

3.5 Sample Size

Our aim was to recruit all hypothermic neonates admitted to the NU who fulfilled the study's inclusion criteria over the study period. The average monthly admission from labour ward to NU was 40 babies, we anticipated 75% of the babies to be hypothermic, with a desired precision estimate of 0.05, and confidence level of 0.95 and an estimated population size of 192 we anticipated a sample size of 116.

3.4 Ethical Consideration

This study was an observational study so not intervention was done. Written informed consent was obtained from the mother so that we could use the data gathered. Ethics approval was awarded by the University of Malawi College of Medicine Research Ethics Committee (COMREC case number: P.O9/17/2272).

3.5 Data Management

All neonates had a temperature recorded within 15 minutes of delivery and on admission to NU. Temperatures were recorded using a digital axillary thermometer (brand name: KAREMAX [calibration was not needed] these are kept at the nursing station), which is the standard of care in the NU, temperature was read after 5 minutes of placement. Babies were recruited following admission into the NU. Anonymised data was collated from the standard daily observation charts. For the first 24 hours of admission this comprised 4 hourly vital signs (temperature, heart rate, respiratory rate, oxygen saturation) and 6 hourly blood glucose checks. For the remainder of the admission it comprised 4 hourly vital signs, 12 hourly blood glucose checks and daily weight check, in accordance with standard practice in the NU, Malawi Standard Treatment Guidelines and the Paediatrics and Child Health Department protocol book. Patients were reviewed by a clinician twice a day or as determined by their clinical condition. Demographic information, concomitant conditions, clinical course and outcome were also recorded on the anonymised case report form. Daily environmental temperature readings were taken on both the NU and labour ward. The WHO definition for hypothermia (<36.5˚C) was adopted for this study.

3.5.1 Statistical Analysis

Descriptive statistics were shown as frequencies and percentages, or as a mean (± standard deviation (SD), as appropriate. Linear regression analyses were conducted using Stata v.15 (Statacorp, College Station, TX) and odds ratios (OR) were calculated after controlling for potential confounders prematurity, sex, and low Apgar scores at 1 minute. P values ≤0.05 were considered statistically significant.

CHAPTER 4: RESULTS

A total of 120 neonates were recruited between August 2018 and March 2019. Eight neonates were lost to follow up, meaning 112 completed files were included for analysis. Maternal median age was 25 years, and 13% were HIV positive (Table 1). Of the neonates, 48% were male, 39% were low birth weight (<2.5kg) and 16% were very low birth weight (<1.5kg) (Table 2). Seventy-four percent of neonates had hypothermia 5 minutes after birth, 77% on admission to NU, 31% at 6 hours, 29% at 12 hours, and 38% at 24 hours (Table 4). Drying after delivery was documented in 96% of cases, 7% received skin-to-skin contact, 4% breastfed immediately after birth, and less than half received KMC, their own bedding or hat (46%, 34% and 42% respectively (Table 3).

The two most common comorbidities were respiratory distress syndrome (RDS, 38%) and transient tachypnea of the newborn (23%). Over half of the subjects (57%) required oxygen support during their hospital stay, which was a mean of 5.5 days (±6.3 days; table 5). Fifteen neonates died (14%), and this number was higher among lower birth weight neonates with hypothermia (Figure 1). Among the neonates, 38% of the neonates were hypothermic on their last temperature reading before discharge or death.

Neonates who were hypothermic 5 minutes after birth were more likely to have hypothermia on admission to the NU compared to those that were normothermic (85% v. 15%, $p<0.01$), more likely to have RDS (88% v. 12%, $p<0.01$); more likely to receive KMC (84% v. 16%, $p=0.02$); more likely to be provided a hat (85% v. 15%, $p=0.02$); and more likely to have a longer hospital stay (87% v. 13%, $p=0.03$). Compared to those that were normothermic on admission, neonates with hypothermia on admission to the NU were more likely to have a diagnosis of transient tachypnoea of the newborn (62% v. 38%, $p=0.04$) and to receive oxygen supplementation (86% v. 14%, p=0.01). Longer hospital stay was documented among neonates with hypothermia on admission to NU (86% v. 14%), although this was not statistically significant. All the neonates who died had hypothermia on admission (100% v. 0%, p=0.02; tables 7,8)

At 24 hours of life, the only significant association with neonatal hypothermia was birth asphyxia (0% v. 100%, p=0.02). Neonates that were provided their own hat in the NU were less likely to have hypothermia at 24 hours (49% v. 51%), although this was not statistically significant. Hypothermia at 24 hours inversely correlated with longer hospital stay (36% v. 64%) and hospital mortality (29% v. 71%), although again neither were statistically significant (table 7,8).

Regarding mortality, hospital deaths were significantly associated with low Apgar scores <6 at one (73% v. 63%, p<0.01) and ten minutes (36% v. 7%, p<0.01), hypothermia on admission to the NU (100% v. 72%, p=0.02), RDS (60% v. 32%, p=0.04), birth asphyxia (27% v. 9%, p=0.04), and receipt of respiratory support (p<0.01). A higher proportion of neonates who died had hypothermia at 5 minutes (87% v. 29%); however, this was not statistically significant (Tables 6,7, and 9).

After adjusting for low Apgar scores at 1 minute, prematurity and sex, hypothermia 5 minutes after birth had an OR of 13.31 (95% CI 4.17-42.54) for hypothermia on admission to the NU, and hypothermia on admission to the NU had an OR of 0.05 (95% CI 0.02-1.25) for receipt of CPAP. Apgar scores <6 at 1 minute had an OR of 5.66 (95% CI 1.55-20.70) for hospital mortality (Table 11), and receipt of CPAP had an OR of 0.05 (95% CI 0.009-0.31) for mortality.

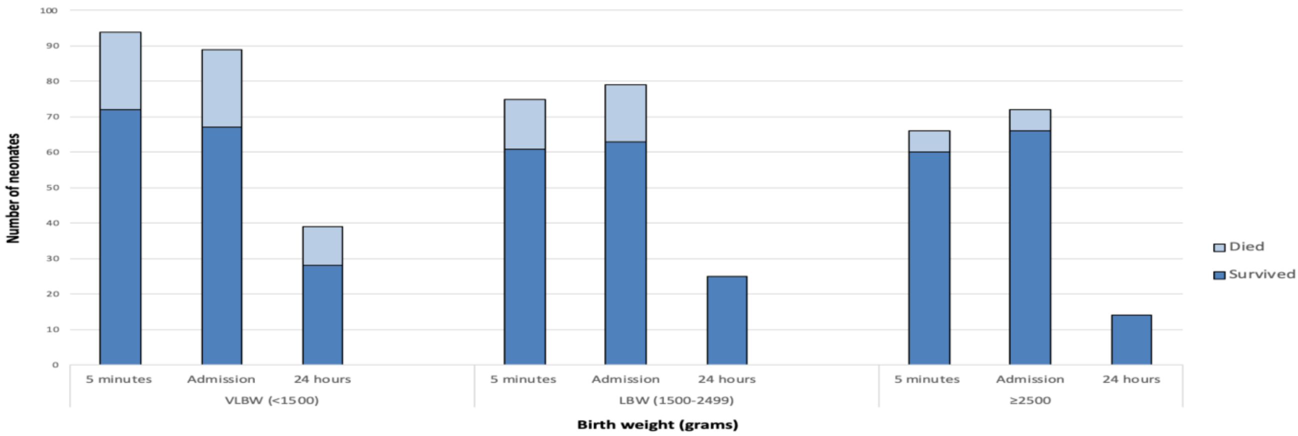

Figure 1. **Frequency of hypothermia at 5 minutes, on admission to NICU, and at 24 hours, by birth weight, stratified by those that died v. survived**

LBW, low birth weight; VLBW, very low birth weight

Table 1 Maternal Characteristics

	N=112
Maternal characteristics	
Maternal age, years (median, SD)	25 (6.8)
Maternal HIV status (%)	
Infected	14 (13)
Unknown	1 (0.9)
Mode of delivery (%)	
Caesarean section	34 (31)
Types of pregnancy (%)	
Singleton	98 (88)
Antenatal visits (%)	
4 complete visits	31 (30)
≤3 antenatal visits	71 (69)
Prematurity (%)	34 (31)
Steroid use in pregnancy (%)	14 (13)
Prolonged rupture of membranes (%)	11 (10)
Infection during pregnancy (%)	5 (4)
Hypertension in pregnancy (%)	13 (12)

Table 2 Neonatal Characteristics

Male (%)	54 (48)
HIV Exposed (%)	14 (13)
Low birth weight (<2.5 kg, %) Very low birth weight (<1.5kg, %)	62 (55) 18 (16)
Apgar score <6 at 1 minute (%)	47 (42)
Apgar score <6 at 5 minutes (%)	73 (65)
Apgar score <6 at 10 minutes (%)	6 (7)
Small for gestational age (%)	12 (11)
Intrauterine growth restriction (%)	18 (16)

Table 3 Neonatal Iinpatient Care

Drying after delivery (%) Skin-to-skin contact after birth (%) Breastfeeding after birth (%)	108 (96) 8 (7) 4 (4)
Warm transport to nursery (%)	103 (92)
NU room temperature, ˚C, mean (SD)	29.3 (1.4)
Glucose level on admission, mg/dL, mean (SD)	102.8 (34.5)
Received kangaroo mother care (%) Provided own bedding (%) Provided own clothing (%) Provided own hat (%)	51 (46) 49 (44) 38 (34) 47 (42)

Table 4 Neonatal Hyperthermia Prevalence

Hypothermia (%)	
5 minutes after birth	83 (74)
On admission to neonatal unit	86 (77)
6 hours after admission	19/62 (31)
12 hours after admission	13/45 (29)
24 hours after admission	24/63 (38)
Before death/discharge	40/105 (38)

Table 5 Neonatal Duration of Stay, Morbidity and Mortality

Neonatal comorbidity (%)	
Respiratory distress syndrome	42 (38)
Transient tachypnea of the newborn	26 (23)
Birth asphyxia	12 (11)
Neonatal sepsis with use of antibiotics	34 (30)
Neonatal jaundice	8 (7)
Meconium aspiration	11 (10)
Respiratory support (%)	
Oxygen supplementation	63 (57)
Continuous positive airway pressure	18 (16)
Neonatal outcomes	
Length of admission, days, mean (SD)	5.5 (6.3)
Hospital mortality (%)	15 (14)

Table 6 Association between Neonatal Hypothermia at 5 Minutes, on Admission to Neonatal Unit and at 24 Hours, and Perinatal Characteristics

	At 5 minutes			**On admission**			**At 24 hours**		
	Present (N=83)	Absent (N=29)	p-value	Present (N=86)	Absent (N=25)	p-value	Present (N=24)	Absent (N=29)	p-value
Perinatal characteristics (%)									
Caesarean section	24/34 (71)	10/34 (29)	0.62	24/34 (71)	10/34 (29)	0.34	8/18 (44)	10/18 (56)	0.60
Prematurity	29/34 (85)	5/34 (15)	0.07	28/34 (82)	6/34 (18)	0.36	11/24 (36)	13/24 (54)	0.32
Gestational age <34 weeks	49/62 (79)	13/62 (21)	0.19	49/62 (79)	13 (21)	0.53	15/38 (39)	23/38 (61)	0.78
Low birth weight <2.5 kg	33/44 (75)	11/44 (44)	0.06	50/62 (81)	12/62 (19)	0.35	17/40 (43)	23/40 (58)	0.63
Very low birth weight <1.5 kg	17/18 (94)	1/18 (6)	0.06	16/18 (89)	2/18 (11)	0.35	7/16 (44)	9/16 (56)	0.63
Apgar score < 6 at 1 minute	32/47 (68)	15/47 (32)	0.22	40/47 (85)	7/47 (15)	0.08	8/24 (33)	16/24 (67)	0.54
Apgar score < 6 at 5 minutes	51/73 (70)	22/73 (30)	0.16	59/73 (81)	14/73 (19)	0.17	15/44 (34)	29/44 (66)	0.32
Apgar score <6 at 10 minutes	5/6 (83)	1/6 (17)	0.51	6/6 (100)	0/6 (0)	0.12	0/2 (0)	2/2 (100)	0.29

Table 7 Association between Neonatal Hypothermia at 5 Minutes, on Admission to Neonatal Unit and at 24 Hours, and Neonatal Comorbidity

	At 5 minutes			**On admission**			**At 24 hours**		
	Present (N=83)	Absent (N=29)	p-value	Present (N=83)	Absent (N=29)	p-value	Present (N=83)	Absent (N=29)	p-value
Neonatal comorbidity (%)									
Hypothermia on admission to neonatal unit	73/86 (85)	13/86 (15)	<0.01	-	-	-	19/52 (37)	33/52 (63)	0.58
Suspected sepsis	21/28 (75)	7/28 (25)	0.90	22/28 (79)	6/28 (21)	0.80	6/23 (26)	17/23 (74)	0.14
Respiratory distress syndrome	37/42 (88)	5/42 (12)	<0.01	35/42 (83)	7/42 (17)	0.20	15/33 (45)	18/33 (55)	0.21
Birth Asphyxia	9/12 (75)	3/12 (25)	0.94	11/12 (92)	1/12 (8)	0.20	0/8 (0)	8/8 (100)	0.02

Table 8 Association between Neonatal Hypothermia at 5 Minutes, on Admission to Neonatal Unit and at 24 Hours, and Inpatient Care

	At 5 minutes			**On admission**			**At 24 hours**		
	Present (N=83)	Absent (N=29)	p-value	Present (N=83)	Absent (N=29)	p-value	Present (N=83)	Absent (N=29)	p-value
Inpatient care (%)									
Received O_2	53/63 (84)	10/63 (16)	<0.01	54/63 (86)	9/63 (14)	0.01	16/43 (37)	27/43 (63)	0.83
Received CPAP	16/18 (89)	2/18 (11)	0.12	17/18 (94)	1/18 (6)	0.05	6/16 (38)	10/16 (63)	0.96
Received kangaroo mother care	43/51 (84)	8/51 (16)	0.02	42/51 (82)	9/51 (18)	0.20	15/36 (42)	21/36 (58)	0.50
Provided own bedding	39/49 (80)	10/49 (20)	0.24	40/49 (82)	9/49 (18)	0.26	17/37 (46)	20/37 (54)	0.12
Provided own clothing	30/38 (79)	8/38 (21)	0.40	29/38 (76)	9/38 (24)	0.93	15/32 (47)	17/32 (53)	0.15
Provided own hat	40/47 (85)	7/47 (15)	0.02	40/47 (85)	7/47 (15)	0.08	17/35 (49)	18/35 (51)	0.06

Table 9 Association between Neonatal Hypothermia at 5 Minutes, on Admission to Neonatal Unit and at 24 Hours, and Neonatal Outcomes

	At 5 minutes			**On admission**			**At 24 hours**		
	Present (N=83)	Absent (N=29)	p-value	Present (N=83)	Absent (N=29)	p-value	Present (N=83)	Absent (N=29)	p-value
Neonatal outcomes (%)									
Duration of stay >5 days	32/37 (86)	5/37 (14)	0.03	32/37 (86)	5/37 (14)	0.08	12/33 (36)	21/33 (64)	0.77
Hospital mortality	13/15 (87)	2/15 (13)	0.20	15/15 (100)	0/15 (0)	0.02	2/7 (29)	5/7 (71)	0.53

Table 10 Neonatal Mortality and Association with Clinical Features and Management

Characteristic	Died (N =15)	Survived (N =93)	p-value
Perinatal characteristics (%)			
Prematurity	9 (60)	41 (44)	0.25
Low Birth Weight <2.5 kg	11 (74)	47 (51)	0.47
Very low birth weight <1.5kg	4 (27)	12 (13)	0.19
Apgar score < 6 at 1 minute	11 (73)	59 (63)	<0.01
Apgar score < 6 at 5 minutes	12 (80)	34 (37)	0.21
Apgar score <6 at 10 minutes	5/14 (36)	1/70 (7)	<0.01
Neonatal comorbidity			
Hypothermia at 5 mins	13 (87)	27 (29)	0.20
Hypothermia on admission to neonatal unit	15 (100)	67 (72)	0.02
Hypothermia at 24 hours	2 (29)	22 (41)	0.54
Hypothermia before discharge	4/13 (31)	36/89 (40)	0.50
Suspected sepsis	2 (13)	25 (27)	0.26
Respiratory distress syndrome	9 (60)	30 (32)	0.04
Birth Asphyxia	4 (27)	8 (9)	0.04
Transient tachypnea of the newborn	0 (0)	26 (28)	0.02
Inpatient care (%)			
Respiratory support			
O_2	15 (100)	45 (48)	<0.01
CPAP	7 (47)	9 (10)	<0.01
Received kangaroo mother care	5 (33)	44 (47)	0.31
Provided own bedding	7 (47)	39 (42)	0.73
Provided own clothing	3 (20)	33 (35)	0.24
Provided own hat	4 (27)	41 (44)	0.20
Outcomes (%)			
Duration of stay >5 days	4 (27)	31 (33)	0.61

Table 11 Multivariable Analysis of Association between Hypothermia, Comorbidity and Outcomes

Outcome	Unadjusted OR (95% CI)	Adjusted[a] OR (95% CI)
Hypothermia 5 minutes after birth		
Low birth weight	2.15 (1.10-4.19)	2.17 (0.91-5.18)
Hypothermia on NU admission	8.98 (3.35-24.09)	13.31 (4.17-42.54)
RDS	0.26 (0.09-0.74)	0.26 (0.07-0.99)
Receipt of O2	0.30 (0.12-0.72)	0.32 (0.13-0.84)
Receipt of KMC	0.35 (0.14-0.89)	0.38 (0.12-1.21)
Hypothermia on NU admission		
Receipt of O2	0.31 (0.13-0.79)	0.34 (0.12-0.94)
Inpatient neonatal mortality		
Apgar score <6 at 1 minute	4.77 (1.34-16.16)	5.66 (1.55-20.70)
CPAP	0.12 (0.03-0.45)	0.05 (0.009-0.31)

CI, confidence interval; CPAP, continuous positive airway pressure; KMC, kangaroo mother care; NU, neonatal unit; OR, odds ratio

[a]Adjusted for Apgar score <6 at 1 minute, prematurity, sex

CHAPTER 5: DISCUSSION

The incidence of hypothermia 5 minutes after birth was extremely high and associated with hypothermia on admission to the NU, RDS, receipt of oxygen supplementation, receipt of KMC and of own hat, and longer hospital stay. Hypothermia on admission was associated with receipt of oxygen supplementation and death. The only significant association identified with hypothermia at 24 hours was birth asphyxia.

These results demonstrate the high incidence of hypothermia in our setting and that this issue affects a larger population beyond those that are preterm and low birth weight. These findings support previous studies that highlight the importance of thermal care in the newborn in the immediate period after birth. In other settings, hypothermia on admission to neonatal units was associated with a 1.26 to 1.72-fold greater risk for hospital mortality [11,7]. In recognition of the importance of neonatal hypothermia as a risk factor for neonatal morbidity and mortality, WHO introduced practical guidelines for clinicians in 2007 for thermal protection. These emphasise the need for drying the baby immediately after birth, skin-to-skin contact with the mother and immediate breastfeeding. In addition, newborns should be wrapped in a warm cloth and given a hat, and provided warm transportation during transfer from delivery room to the NU [6]. A study in Brazil by de Almeida MF et al demonstrated that use of plastic bag/wrap independently decreased chances of hypothermia at 5 minutes by 47% in preterm infants, and a Cochrane review done by McCall EM *et al*. [12] in 2010 found that hypothermia on admission decreased by 34% in preterm infants with gestational age <28 weeks when a plastic bag wrap was used soon after birth. In preterm infants, the use of a cotton cap after birth decreased hypothermia on admission [7].

In our cohort, we documented drying after delivery in 96% of cases, but only 7% received skin-to-skin contact and 4% breastfed immediately after birth. We did not have sufficient numbers to evaluate the association of these interventions with mortality. Despite the low-resource setting of this study (lack of heating in delivery room, environmental temperature optimised only for the mother and staff, poor hypothermia prevention on delivery, poor baby wrapping, lack of heated transportation to the NU), these results highlight an opportunity for simple, low cost interventions that can impact clinical outcome.

While evaluating KMC, hypothermia at 5 minutes after birth was associated with an OR of 0.34 for receipt of KMC, but after adjusting for potential confounders the association was no longer significant. It may have been that hypothermia reflected other comorbidities that required more intensive monitoring, and therefore KMC could not be practiced; another possibility is that staff shortages mean these results reflect a continuum of resource-constrained care. In particular, KMC has been shown to be a viable intervention for treating hypothermia, and more importantly is a low-cost measure in our setting since we have lack of other thermal care resources (warmed incubator transportation, plastic wrap, enough radiant warmers). A study done by Vesel L et al in 2015 [13] on the implementation of KMC in low resource countries in Africa showed that KMC could be used for management of low birth weight babies. A multicountry randomised-controlled trial in Africa is currently evaluating the effect of immediate KMC on neonatal survival, and may provide more evidence to support the use of KMC in preventing neonatal hypothermia in low resource settings.

The statistically significant association between low Apgar scores <6 with hospital mortality reaffirms the importance of management during delivery in determining neonatal outcomes. In our setting, management of preterm infants is still lacking (no use of plastic bags, no surfactant treatment available, lack of incubators, intubation not commonly available for preterm infants). A lack of skilled healthcare workers in hospitals mean that there are insufficient staff to adequately care for the mother and newborn after delivery, affecting the quality and competence of neonatal resuscitation. Reducing the incidence of hypothermia among preterm and low birth weight infants has been evaluated in other studies [14,15]; however, while roughly 31-55% of our patients were preterm and/or had low birth weight, over 70% of neonates were hypothermic at 5 minutes and on admission to the NU, indicating that there is a generally high incidence of hypothermia affecting newborns in low resource settings such as these. However, thermal care is part of basic newborn care and, if done well, can have an impact on outcomes. Therefore, reduction of neonatal mortality in countries such as Malawi can be attained through optimization of these simple measures.

The most common neonatal morbidities associated with hypothermia were RDS and birth asphyxia, and hypothermia 5 minutes after birth was associated with a 74% lower risk of RDS, although this association was weak after adjusting for potential confounders. Contrary to other studies, which noted the association between hypothermia and RDS in low birth weight and preterm infants [14,15], we instead found that hypothermia 5 minutes after birth had an OR of 0.26 for RDS, although this association was weaker after adjusting for potential confounders (adjusted OR 0.26 (95% CI 0.07-0.99)). Both hypothermia 5 minutes after birth and on admission to the NU had an OR of 0.31 and 0.32, respectively, for receipt of oxygen supplementation, although these associations were also weak after adjusting for potential confounders. These findings may reflect the constraints of staffing shortages; however, as the sample size was small, all results should be interpreted with caution. We documented, for both hypothermia at 5 minutes and on admission, a higher proportion of CPAP usage in both groups, although neither reached statistical significance.

The study is limited by the modest size of our sample size, which made it difficult to identify clear associations between variables, and also means that all results should be interpreted with caution. Although every effort was made to compile a complete dataset, we still had missing data, especially with labour ward temperature, and duration of time between transport from the delivery room to the NU. We did not document maternal temperature, and low staffing levels on the labour ward and NU meant there were challenges with the collection of daily observations. Of note this study was conducted during different seasons, so weather would be another confounder which should be considered. Despite these limitations, this study provides one of the most detailed recent studies on neonatal hypothermia conducted in a low resource setting. Furthermore, we did adjust for potential confounders, and identified potential associations and interventions of significance. We identified a strong association with mortality among all neonates with hypothermia on admission to the NU; however, as all neonates who died had documented hypothermia on admission, we were unable to calculate an odds ratio.

CHAPTER 6: CONCLUSION

There is a high incidence of hypothermia that affects the majority of neonates at our tertiary-level hospital, which was similar to finding in studies done in surrounding countries Zambia and Zimbabwe [9,10]. Hypothermia at 5 minutes was associated with an OR of 13.31 for hypothermia on admission to the NU, which was itself significantly associated with mortality. Our findings reiterate the vital importance of addressing the immediate period after birth, and suggest that the use of simple interventions in the immediate period after delivery (plastic bags for Low birthweight babies, higher delivery room temperatures, better transportation equipment) prior to arrival in the neonatal unit could improve neonatal hypothermia, and reduce associated morbidity and mortality.

REFERENCES

1. Blencowe H, Vos T, Lee ACC, Philips R, Lozano R, Alvarado MR, et al. Estimates of neonatal morbidities and disabilities at regional and global levels for 2010: introduction, methods overview, and relevant findings from the Global Burden of Disease study. *Pediatric Research*. 2013;74(1):4-16. Retrieved from: https://dx.doi.org/10.1038/pr.2013.203
2. Hug L, Sharrow D. Levels and Trends in Child Mortality: Report 2017. UNICEF; 2017. Retrieved from https://www.unicef.org/reports/levels-and-trends-child-mortality-report-2017 [Accessed 20th April 2018]
3. Rajaratnam JK, Marcus JR, Flaxman AD, Wang H, Levin-Rector A, Dwyer L, et al. Neonatal, postneonatal, childhood, and under-5 mortality for 187 countries, 1970-2010: a systematic analysis of progress towards Millennium Development Goal 4. *The Lancet*. 2010;375(9730):1988-2008. Retrieved from https://dx.doi.org/10.1016/S0140-6736(10)60703-9
4. Lawn JE, Cousens S, Zupan J. Neonatal Survival 1 4 million neonatal deaths: When? Where? Why? *Lancet*. 2005; 365(1):891-900. Retrieved from https://doi.org/10.1016/S0140-6736(05)71048-5
5. NSO. *Malawi Demographic and Health Survey 2015-16.* Zomba: National Statistics Office; 2017. pp 1-658. Retrieved from http://dhsprogram.com/pubs/pdf/FR319/FR319.pdf
6. Dragovich D, Tamburlini G, Alisjahbana A, Kambarami R, Karagulova J, Lincetto O, et al. Thermal control of the newborn: Knowledge and practice of health professionals in seven countries. *Acta Paediatric*, *International Journal of Paediatrics.* 1997; 86(6):645-650. Retrieved from https://dx.doi.org/10.1111/j.1651-2227.1997.tb08949.x
7. De Almeida MFB, Guinsburg R, Sancho GA, Rosa IRM, Lamy ZC, Martinez FE, et al. Hypothermia and early neonatal mortality in preterm infants. *Journal of Pediatrics*. 2014;164(2):271-275. Retrieved from https://doi.org/10.1016/j.jpeds.2013.09.049

8. Miller SS, Lee HC, Gould JB. Hypothermia in very low birth weight infants: Distribution, risk factors and outcomes. *Journal of Perinatology*. 2011(31):S49-S56. Retrieved from https://dx.doi.org/10.1038/jp.2010.177

9. Christensson K, Bhat GJ, Eriksson B, Shilalukey-ngoma MP, Sterky G. The effect of routine hospital care on the health of hypothermic newborn infants in Zambia. *Journal of Tropical Pediatrics*. 1995;41(4):210-214. Retrieved from https://doi.org/10.1093/tropej/41.4.210

10. Kambarami RA, Mutambirwa J, Maramba PPP. Caregivers' perceptions and experiences of "kangaroo care" in a developing country. *Tropical Doctor*. 2002;32(3):131-133. Retrieved from https://dx.doi.org/10.1177/004947550203200303

11. Costeloe K, Hennessy E, Haider S, Stacey F, Marlow N, Draper E, et al. Short term outcomes after extreme preterm birth in England: comparison of two birth cohorts in 1995 and 2006 (the EPICure studies). *BMJ (Online).* 2012;345:e7976. Retrieved from https://doi.org/10.1136/bmj.e7976

12. McCall EM, Alderdice F, Halliday HL, Jenkins JG, Vohra S. Interventions to prevent hypothermia at birth in preterm and/or low birthweight infants. *Cochrane Database of Systematic Reviews*; 2010. Retrieved from https://dx.doi.org/10.1002/14651858.cd004210.pub4

13. Vesel L, Bergh AM, Kerber KJ, Valsangkar B, Mazia G, Moxon SG, et al. Kangaroo mother care: a multi-country analysis of health system bottlenecks and potential solutions. *BMC Pregnancy and Childbirth*. 2015;15(S2):S5. Retrieved from https://dx.doi.org/10.1186/1471-2393-15-S2-S5

14. Jensen CF, Ebbesen F, Petersen JP, Sellmer A, Bach CC, Henriksen TB. Hypothermia at neonatal intensive care unit admission was not associated with respiratory disease or death in very preterm infants. *Acta Paediatrica, International Journal of Paediatrics.* 2017;106(12):1934-1939. Retrieved from https://dx.doi.org/10.1111/apa.13998

15. Lyu Y, Shah PS, Ye XY, Warre R, Piedboeuf B, Deshpandey A, et al. Association between admission temperature and mortality and major morbidity in preterm infants born at fewer than 33weeks' gestation. *JAMA Pediatrics*. 2015;169(4):2-7. Retrieved from https://dx.doi.org/10.1001/jamapediatrics.2015.0277