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HYPOTHERMIA AMONG NEONATES ADMITTED TO THE NEONATAL UNIT AT A TERTIARY HOSPITAL IN SOUTH AFRICA

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A research report submitted to the Faculty of Health Sciences, University of the Witwatersrand, Johannesburg, in partial fulfilment of the requirements for the degree of Master of Medicine
Johannesburg, 2019

DECLARATION

I, Jacqueline Ng'eny declare that this research report is my own, unaided work. It is being submitted for the Degree of Master of Medicine, Paediatrics at the University of the Witwatersrand, Johannesburg. It has not been submitted before for any degree or examination at any other University.

(Signature of Candidate)

9th day of June 2020

Name of Primary Supervisor: Sithembiso Velaphi

Signature of Primary Supervisor: _____; Date: 15 June 2020

DEDICATION

To my family,

For all their support

PRESENTATIONS ARISING FROM THIS STUDY

1. University of Witwatersrand, Department of Paediatrics Research Day: December 2017

2. 38th Conference on Priorities in Perinatal Care in Southern Africa, Western Cape: March 2019

PUBLICATIONS ARISING FROM THIS STUDY

Ng'eny JC, Velaphi S. Hypothermia among neonates admitted to the neonatal unit at a tertiary hospital in South Africa. Journal of Perinatology: Official Journal of the California Perinatal Association. 2019 Oct DOI: 10.1038/s41372-019-0539-y.

ABSTRACT

Objectives: To determine the prevalence of hypothermia on admission and at 24 hours of life in very low birth weight infants (VLBWI) and associated morbidity and mortality.

Study design: Hospital records of VLBWI admitted to a neonatal unit were reviewed for information on patient body temperature, clinical characteristics and mortality. Comparisons between normothermic and hypothermic VLBWI were performed.

Results: Mean gestational age and birth weight of enrolled infants were 29 ± 3 weeks and 1140 ± 253 g, respectively. Prevalence of admission hypothermia was 46.1%, with 38% developing hypothermia within 24-h following admission. VLBWI with hypothermia were more likely to have been born vaginally [aOR 2.85 (1.37–5.91)], have a birth weight < 1000 g [aOR 2.28 (1.25–4.16)], required resuscitation at birth [aOR 2.20 (1.23–3.94)], develop metabolic acidosis [aOR 3.04 (1.35–6.84)] and die within the first week of life [aOR 4.79 (1.43–16.02)]

Conclusions: Prevalence of hypothermia in VLBWI is high, and is associated with poor outcomes.

ACKNOWLEDGEMENT

I acknowledge the work done by the clinical staff at the Chris Hani Baragwanath Academic Hospital neonatal unit, and the records department for assistance in retrieval of the medical records.

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LIST OF ABBREVIATIONS

aOR	Adjusted odds ratio
CPR	Cardiopulmonary resuscitation
CHBAH	Chris Hani Baragwanath Academic Hospital
CI	Confidence interval
HIC	High-income countries
HREC	Human Research Ethics Committee
ICU	Intensive care unit
IVH	Intraventricular haemorrhage
KMV	Kangaroo mother care
LMIC	Low- and middle-income countries
OR	Odds ratio
SD	Standard Deviation
TICU	Transitional ICU-TICU)
VLBW	Very low birth weight
VLBWI	Very low birth weight infants
WHO	World Health Organisation

PUBLISHED MANUSCRIPT IN MS-WORD

INTRODUCTION

Very low birth weight infants (VLBWI) have impaired temperature regulatory mechanisms that predispose them to hypothermia. This predisposition is mainly due to high surface-area-to-mass ratio, reduced subcutaneous adipose tissue, a thin stratum corneum and inadequate brown fat [1–3]. Neonatal hypothermia (temperature below 36.5 °C) increases the risk of mortality by 28% for every 1 °C drop in body temperature [4]. Hypothermia also increases the likelihood of developing morbidities like sepsis, metabolic acidosis, respiratory distress, hypoglycaemia and intraventricular haemorrhage (IVH) [5–7].

The prevalence of hypothermia among VLBWI in high-income countries (HIC) ranges from 53.4 to 76.7% [8–11]. There are few studies from low- and middle-income countries (LMIC) that have reported on prevalence of hypothermia on VLBWI despite high burden of preterm births in these countries [12–14]. Hypothermia in VLBWI most likely plays a major role in high neonatal mortality rate observed in LMIC. We therefore determined the prevalence of hypothermia in VLBWI, and assessed the short-term outcomes of hypothermic VLBWI in a neonatal unit in a public tertiary hospital from LMIC

PATIENTS AND STUDY MATERIAL

Study design and setting

We conducted a retrospective chart review of VLBWI (birth weight < 1500 g) admitted into the neonatal unit at Chris Hani Baragwanath Academic Hospital (CHBAH) from 1st January to 31st December 2016. CHBAH is a public tertiary hospital located in Johannesburg, Gauteng Province in South Africa. The hospital serves as a referral centre for Soweto and surrounding areas with an estimated population of two million people. It caters for ~22,000 live births annually, of which 3–5% are VLBWI. To prevent hypothermia, the neonatal unit protocol requires that all preterm and VLBWI are placed under a radiant warmer soon after birth. Infants born at gestation

<30 weeks are placed in a plastic bag without being dried, and others are dried under the radiant warmer. All VLBWI have a hat placed on their heads after drying. On admission to the unit, all VLBWI are nursed in an incubator unless they are on mechanical ventilation in which case they are nursed under an overhead radiant warmer. On admission and every 3 h, all neonates have their skin temperature measured and recorded on a temperature chart.

Study population

The study population included VLBWI admitted into the unit between 1st January and 31st December 2016. Infants who were older than 24 h at the time of admission, those without a documented admission temperature, with major congenital anomalies, and those transferred out to other healthcare facilities within the first 7 days of life, were excluded from the study.

Variables

We defined hypothermia as a skin temperature <36.5 °C. Hypothermic infants were sub-classified into mild hypothermia (36.0–36.5 °C), moderate hypothermia (32.0–36.0 °C) and severe hypothermia (<32.0 °C) [1]. Other data collected included gestational age, antenatal steroid exposure (received at least one dose of antenatal steroids), maternal HIV status, birth weight, sex, mode of delivery (vaginal versus caesarean section), place of birth (inborn versus referrals), need for resuscitation and the 5-min Apgar score. Outcome variables assessed were respiratory distress, hypoglycaemia, metabolic acidosis, IVH, sepsis and death within the first 7 days of life. Need for resuscitation was defined as documentation of an infant requiring assistance with breathing using at least bag and mask ventilation. Respiratory distress referred to increased work of breathing demonstrated by the presence of tachypnea (respiratory rate> 60), chest retractions, nasal flaring or grunting. Metabolic acidosis was present if the pH was <7.25 and/or the base deficit was more than 10 mmol/L on arterial blood gas analysis. Hypoglycaemia was defined as blood glucose

level <2.6 mmol/L. IVH was based on cranial ultrasound findings recorded in the patients' notes by the attending neonatologist. Sepsis was diagnosed if a blood culture grew an organism considered to be a pathogen.

Sample size

We determined the required sample size of 384 using an assumed population prevalence of hypothermia of 62% in VLBWI with a 5% level of precision, a power of 80% and a confidence interval (CI) of 95%. We aimed to collect 480 hospital records of VLBWI to allow for an estimated 30% incomplete data on admission temperature.

Data analysis

Categorical variables were described using frequencies and percentages. Continuous variables were summarised using means with standard deviations or medians with interquartile ranges. In comparing hypothermic and non- hypothermic VLBWI, categorical variables were compared using the chi-squared test or Fisher's exact test, and continuous variables were compared using the Student's *t* test and Wilcoxon rank-sum test. Multivariate analyses was undertaken using the logistic regression model to identify factors associated with hypothermia or poor outcomes among those with hypothermia. Odds ratio (OR) and 95% CI were computed for all outcomes. All statistical analyses were performed using STATA version 13 (Stata Corp LLC). Statistical significance was defined as two-sided p value < 0.05.

RESULTS

Prevalence of hypothermia among VLBWI

Of the 799 VLBWI admitted to the neonatal unit during the study period, 453 (92.3%) were enrolled into the study (Fig. 1). Forty-six percent ($n = 209$) had hypothermia on admission, of whom 53.1% ($n = 111$), 44.5% ($n = 93$) and 2.4% ($n = 5$) had mild, moderate and severe

hypothermia, respectively (Fig. 2). Following admission, 314 infants had temperature records available for the first 24 h of life, with 38% ($n = 120$) of these infants developing hypothermia (Fig. 1).

Characteristics of VLBWI enrolled

Thirty-one percent of sample population ($n = 142$) were HIV exposed, 61% ($n = 257$) received antenatal steroids, 88.7% ($n = 402$) were in-born, 44.6% ($n = 202$) were born by vaginal delivery and 48.6% ($n = 220$) were male (Table 1). The mean (standard deviation) gestational age and birth weight were 29 (±3) weeks and 1140 (±253) grams, respectively. In 15.5% ($n = 64$) of infants, the 5-min Apgar score was <7. Approximately 17% ($n = 79$) of all the infants required resuscitation at birth.

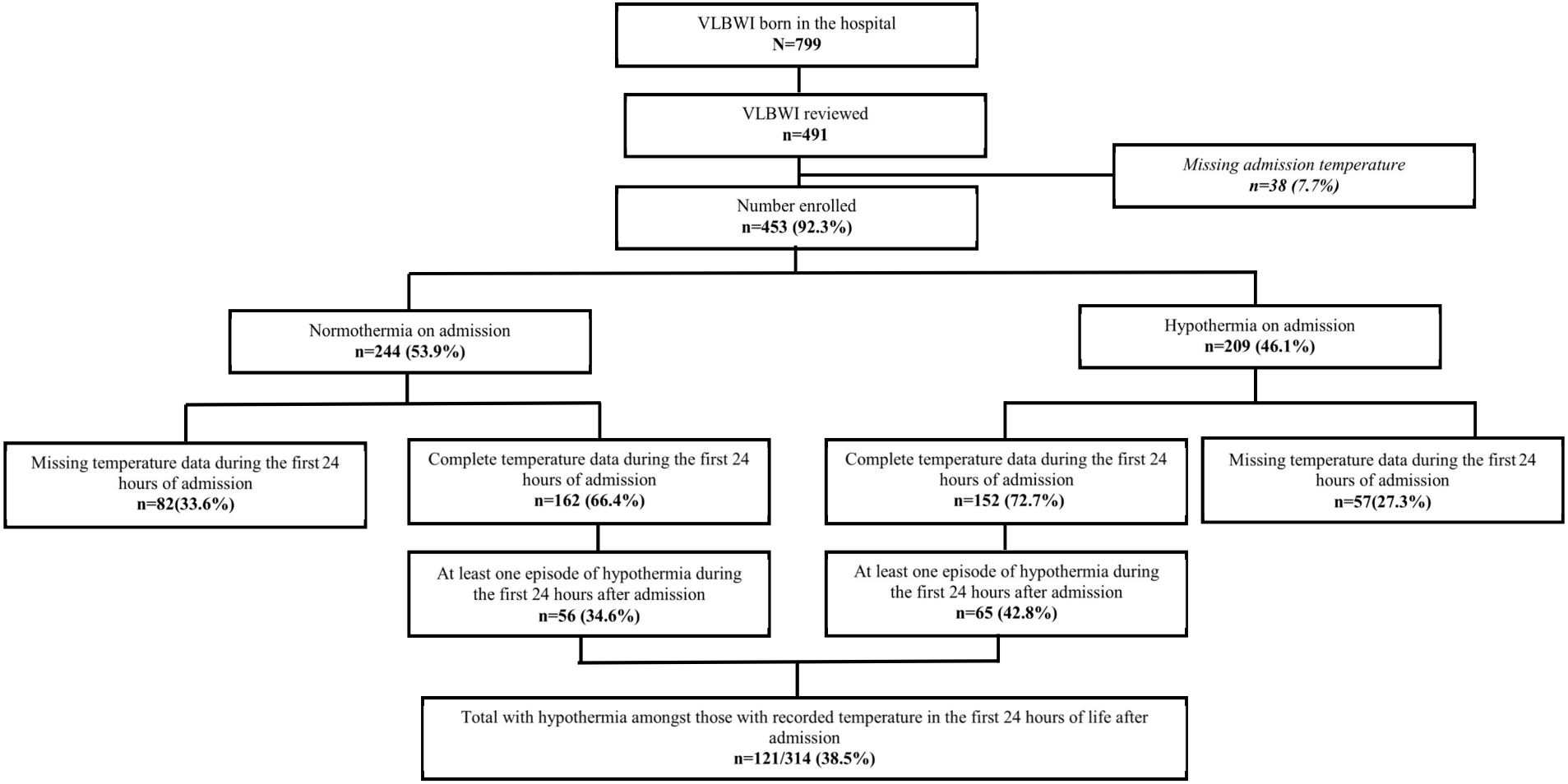

Figure 1. Hypothermia on admission and within the first 24 hours of admission

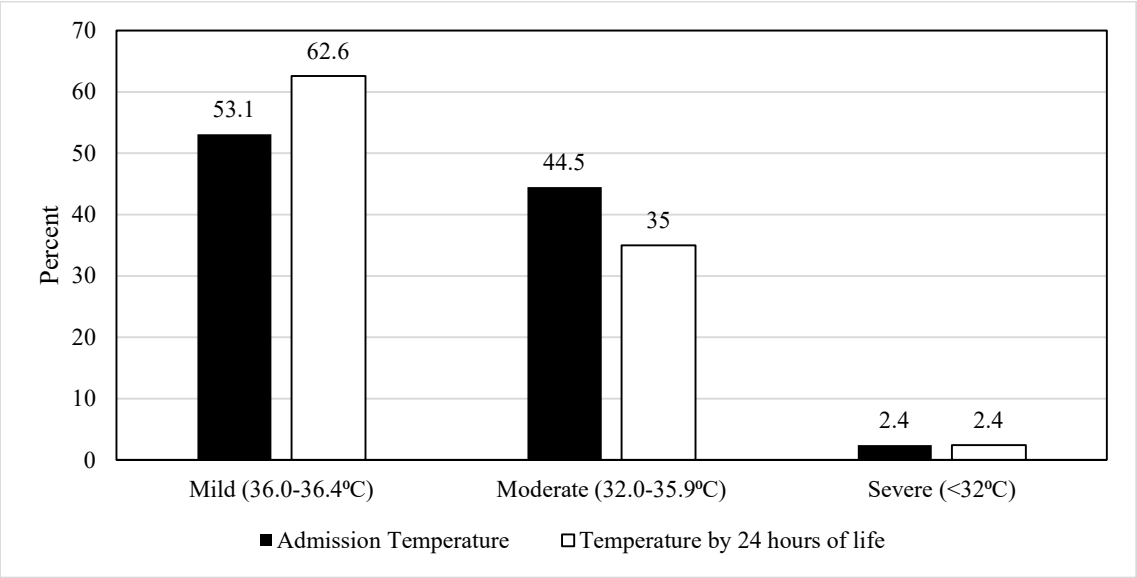

Figure 2. Categories of severity of hypothermia on admission and at 24 hours of life

Table 1.Characteristics of normothermic and hypothermic VLBWI

		All[a] n/N (%)	Normothermic n/N (%)	Hypothermic n/N (%)	Odds Ratio (95% CI)
Sex (Male)		220/453 (48.6)	117/244 (48.0)	103/209 (49.3)	1.05 (0.73 – 1.53)
Gestation	(<30 weeks)	251/451 (55.7)	132/244 (54.1)	119/207 (57.5)	1.15 (0.79 – 1.67)
	Mean±SD	29±3	29±2	29±3	-
Birth weight	(<1000g)	133/453 (29.4)	58/244 (23.8)	75/209 (35.9)	**1.79 (1.19 – 2.70)**
	Mean±SD	1140±253	1173±233	1102±270	-
Maternal HIV Status Positive		142/450 (31.6)	75/244 (30.7)	67/206 (32.5)	1.09 (0.73 – 1.62)
Received Antenatal Steroids		257/421 (61.0)	143/228 (62.7)	114/193 (59.1)	0.86 (0.58 – 1.27)
Inborn		402/453 (88.7)	219/244 (89.8)	183/209 (87.6)	1.24 (0.69 – 2.23)
Vaginal delivery		202/453 (44.6)	98/244 (40.2)	104/209 (49.8)	**1.48 (1.02 – 2.14)**
Apgar at 5 min <7		64/412 (15.5)	32/225 (14.2)	32/187 (17.1)	1.25 (0.73 – 2.12)
Required Resuscitation at birth		79/452 (17.5)	29/243 (11.9)	50/209 (23.9)	**2.32 (1.41 – 3.83)**

[a]Missing values for maternal HIV status (n=3), antenatal steroids (n =32), Apgar at 5min (n=41), gestational age (n = 2);
Bold values indicate statistical significance odds ratio result

Morbidity and mortality outcomes

Overall, 92.5% (n = 418) of the infants had respiratory distress, 27.4% (n = 124) had hypoglycaemia, 42.3% (n =191) had metabolic acidosis and 10% (n = 44) had sepsis. Of the infants who had a cranial ultrasound done, 17.7% (n = 41) had IVH. Ninety-one (20.7%)

infants died within the first 7 days of life, and of these deaths, 20.9% ($n = 19$) occurred within the first 24 h of life (Table 1).

Hypothermic infants were more likely to develop metabolic acidosis [47.4% versus 37.9%, aOR 3.04 (1.35–6.84)] and to die within the first 7 days of life [24.9% versus 17.2%, aOR 4.79 (1.43–16.02)] (Table 2). Severity of hypothermia did not significantly affect the outcomes of hypothermic infants (Table 3).

Table 2. Outcomes associated with admission hypothermia

	All[a] n/N (%)	Normothermic n/N (%)	Hypothermic n/N (%)	OR (95% CI)	aOR (95% CI)
Respiratory distress	418/452 (92.5)	224/243 (92.2)	194/209 (92.8)	1.09 (0.54-2.22)	-
Hypoglycemia	124/452 (27.4)	69/243 (28.4)	55/209 (26.3)	0.90 (0.59-1.36)	-
Metabolic acidosis	191/452 (42.3)	92/243 (37.9)	99/209 (47.4)	**1.48 (1.01-2.15)**	[b]**3.04 (1.35 – 6.84)**
Intraventricular haemorrhage	41/231 (17.7)	24/122 (19.7)	17/109 (15.6)	0.69 (0.37-1.30)	-
Sepsis	44/439 (10)	24/238 (10.1)	20/201 (10)	1.03 (0.56-1.91)	-
Death	91/439 (20.7)	41/238 (17.2)	50/201 (24.9)	**1.59 (1.00-2.53)**	[b]**4.79 (1.43 – 16.02)**

OR odd ratio, *aOR* adjusted odds ratio

[a]Missing values: respiratory distress ($n = 1$) hypoglycaemia ($n = 1$) metabolic acidosis ($n = 1$) IVH ($n = 204$), sepsis ($n = 14$), death ($n = 14$)

[b]Adjusted for mode of delivery, birth weight, resuscitation at birth

Table 3. Prevalence of adverse events in VLBWI according to severity of hypothermia

	All Hypothermic[a] n/N (%)	Mild Hypothermic n/N (%)	Moderate to Severe Hypothermic n/N (%)	OR (95% CI)
Respiratory distress	194/209 (92.8)	100/111 (90.1)	94/98 (95.9)	2.59 (0.80 – 8.40)
Hypoglycemia	55/209 (26.3)	32/111 (28.8)	23/98 (23.5)	0.76 (0.41 – 1.41)
Metabolic acidosis	99/209 (47.4)	47/111 (42.3)	52/98 (53.1)	1.54 (0.89 – 2.66)
Intraventricular haemorrhage	17/109 (15.6)	8/59(13.6)	9/50(18.0)	1.40 (0.50 – 3.95)
Sepsis	20/201 (10)	11/109 (10.1)	9/92 (9.8)	0.97 (0.38 – 2.44)
Death	50/201 (24.9)	21/109 (19.3)	29/92 (31.5)	1.93 (1.01 – 3.69)

OR odds ratio

[a] Missing values: IVH (n=100), sepsis(n=8), death(n=8);

Predictors of admission hypothermia in VLBWI

Hypothermic VLBWI were most likely to have been born vaginally [aOR 2.85 (1.37–5.91)], have a birth weight < 1000 g [aOR 2.28 (1.25–4.16)] and have required resuscitation at birth [aOR 2.20 (1.23–3.94)] (Table 4).

Table 4. Predictors of admission hypothermia among VLBWI

	OR (95% CI)	aOR (95% CI)
Mode of delivery(vaginal)	**1.48 (1.02 – 2.14)**	[a]**2.85 (1.37 – 5.91)**
Birth weight(<1000g)	**1.79 (1.19 – 2.70)**	[b]**2.28 (1.25 – 4.16)**
Resuscitation at birth	**2.32 (1.41 – 3.83)**	[c]**2.20 (1.23 – 3.94)**

OR odds ratio, *aOR* adjusted odds ratio, *CI* confidence interval
[a]Adjusted for birth weight, resuscitation at birth [b]Adjusted for mode of delivery, resuscitation at birth [c]Adjusted for birth weight, mode of delivery

Factors associated with mortality in VLBWI

The results of the multivariable analysis are shown in Table 5. Birth weight < 1000 g and resuscitation at birth were significantly associated with mortality [(aOR 15.67 (7.69–31.90) and 4.34 (1.93–9.77)], respectively.

Table 5. Factors associated with mortality in VLBWI

	All[a] n/N (%)	Survived n/N (%)	Died n/N (%)	OR (95% CI)	aOR (95% CI)
Maternal HIV Status (positive)	138/436 (31.7)	105/347 (30.3)	33/89 (37.1)	1.36 (0.83 – 2.21)	-
Received antenatal Steroids	253/408 (62.0)	216/324 (66.7)	37/84 (44.0)	**0.39 (0.24 – 0.64)**	0.54 (0.26 – 1.14)
Inborn	389/439 (88.6)	310/349 (89.1)	79/91 (86.8)	1.24 (0.62 – 2.48)	-
Vagina delivery	193/439 (44.0)	132/348 (37.9)	61/91 (67.0)	**3.33 (2.04-5.42)**	1.25 (0.59 – 2.64)
Sex (Male)	214/439 (49.0)	169/348 (48.6)	45/91 (49.5)	1.04 (0.65 – 1.64)	-
Birth weight (<1000 g)	125/439 (28.5)	55/348 (15.8)	70/91 (76.9)	**17.76 (10.1 – 31.3)**	**15.67 (7.69 – 31.90)**
Apgar at 5 min (<7)	59/398 (14.8)	37/325 (11.4)	22/73 (30.1)	**3.36 (1.83 – 6.15)**	1.06 (0.46 – 2.46)
Hypothermia at admission	201/439 (45.8)	151/348 (43.4)	50/91 (54.9)	**1.59 (1.00 – 2.53)**	0.94 (0.48 – 1.84)
Respiratory distress	407/439 (92.7)	318/348 (91.4)	89/91 (97.8)	4.20 (0.98 – 17.1)	-
Hypoglycemia	120/439 (27.3)	102/348 (29.3)	18/91 (19.8)	0.59 (0.34 – 1.05)	-
Metabolic acidosis	186/439 (42.4)	144/348 (41.4)	42/91 (46.2)	1.21 (0.76 – 1.93)	-
IVH	41/231 (17.8)	25/188 (13.3)	16/43 (37.2)	**2.79 (1.38 – 5.62)**	-
Sepsis	45/439 (10.3)	40/348 (11.5)	5/91 (5.5)	0.45 (017 – 1.17)	-
Required resuscitation at birth	74/439 (16.9)	37/348 (10.6)	37/91 (40.7)	**5.76 (3.36 – 9.88)**	**4.34 (1.93 – 9.77)**

[a]Missing values: maternal HIV status (*n* = 3) *antenatal steroids (*n* = 31) gestation (*n* = 2) *Apgar at 5 min (*n* = 41) IVH (*n* = 208)
OR odds ratio, *aOR* adjusted odds ratio

DISCUSSION

We report a high prevalence of hypothermia among VLBWI on admission to the neonatal unit and at 24 h post admission. A significant proportion of VLBWI who had a normal admission temperature developed hypothermia within the neonatal unit. VLBWI with hypothermia were more likely to weigh < 1000 g, be born vaginally, and to require resuscitation at birth. Hypothermia was also associated with the increased risk of mortality in the first week of life.

The prevalence of admission hypothermia among VLBWI (46.1%) reported in this study is lower than previously reported rates of 53–56% from HIC [8, 9], and 62–93% from LMIC countries [10, 11, 13–15]. Our study was comparable with the cited studies on definition of hypothermia, exclusion criteria, mean gestational age and mode of temperature measurement (axillary). However, in our study, delivery room temperature which may have affected the infant's temperature was not recorded. Furthermore, this study used weight instead of gestational age and thus, it is possible that some of the VLBWI were more mature, but growth restricted therefore less risk for hypothermia.

Persistence or development of hypothermia among VLBWI post admission to the neonatal unit is of concern as it suggests sub-optimal thermal care post admission. Most VLBWI in the unit are nursed in an incubator, and the high incidence of hypothermia post admission implies incubators were inadequate source of heat, either from their incorrect use or their malfunctioning. Incubators have been reported to be less effective in maintaining body temperature in neonates when compared with kangaroo mother care (KMC) [16].

Contrary to other studies, in this study we found that vaginal deliveries were more likely to be hypothermic on admission. The higher rate of hypothermia observed with vaginal compared with caesarean section delivery in this study is most likely due to differences in environmental temperatures. Delivery ward in this study setting is an open hall with cubicles closed with hanging curtains. This design makes it difficult to maintain labour and delivery room temperatures within the recommended temperatures of 25–27 °C. Due to a limited

number of personnel in our institution, fewer number of vaginal deliveries are attended by a healthcare provider whose sole responsibility is to look after the new born baby compared to those born by caesarean section. An infant receiving 100% attention from the healthcare provider after delivery is most likely to receive better thermal care. This finding highlights the importance of having a healthcare provider dedicated to the care of infant at the time of delivery.

The association observed between hypothermia and need for resuscitation is most likely due to infants who required resuscitation having been exposed to the cold environment for longer periods with inadequate temperature control measures during resuscitation.

We found a significant association between hypothermia and presence of metabolic acidosis, and between hypothermia and high mortality. Hypothermia may cause peripheral vasoconstriction and increase oxygen demand leading to anaerobic metabolism with subsequent development of metabolic acidosis [2, 5]. These findings also support previous studies that admission hypothermia is associated with increased risk for mortality [8–10].

Findings from this study highlight the need for more emphasis being placed in thermal care in the first 24 h of life. One such approach involves adopting a ‘thermoregulatory bundle' that includes maintenance of appropriate ambient temperature between 24 and 27 °C in labour and delivery room, training of all midwives in practices of maintaining normal temperature and prevention of heat loss immediately after birth especially during resuscitation [17]. A temperature bundle that includes maintenance of labour and delivery room temperature, wrapping VLBWI in polyethylene bags and putting on cotton caps can also be adopted as it has been shown to reduce incidence of admission hypothermia by 62% [17]. To prevent hypothermia post admission to the neonatal unit, appropriate use of incubators and overhead radiant warmers, avoiding unnecessary exposure of VLBWI, and early use of KMC can be adopted.

Limitation in this study is related to inherent flaws of a retrospective design. Missing data

resulting in exclusion of some infants, and non-random selection (first records to be retrieved were used) might have increased the risk of selection bias. It is therefore possible that the sample is not representative of the general population limiting generalizability of this study's findings. In addition, there was no data on adherence to standards of care to prevent hypothermia, which made it difficult to evaluate the impact of (non) adherence to the standards on the level of hypothermia among the VLBWI. Despite these limitations, the study was adequately powered to detect significant occurrence of hypothermia on admission.

CONCLUSION

Hypothermia among VLBWI is a significant problem that is associated with adverse outcomes. Quality improvement initiatives focusing on prevention of neonatal hypothermia should be implemented in neonatal units. The initiatives should address malfunctioning equipment and advocate for KMC as part of thermoregulatory bundle in the care of VLBWI.

ACKNOWLEDGEMENTS

We acknowledge the work done by the clinical staff at the Chris Hani Baragwanath Academic Hospital neonatal unit, and the records department for assistance in retrieval of the medical records.

CONFLICT OF INTEREST

The authors declare that they have no conflict of interest.

ETHICAL STATEMENT

Ethical approval for the study was received from the University of Witwatersrand Human Research Ethics Committee prior to undertaking the study (Protocol reference number M170540).

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PUBLISHED MANUSCRIPT IN PDF FORMAT

Journal of Perinatology
https://doi.org/10.1038/s41372-019-0539-y

ARTICLE



Hypothermia among neonates admitted to the neonatal unit at a tertiary hospital in South Africa

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Received: 27 March 2019 / Revised: 11 October 2019 / Accepted: 20 October 2019
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Abstract

Objectives To determine the prevalence of hypothermia on admission and at 24 h of life in very low birth weight infants (VLBWI) and associated morbidity and mortality.

Study design Hospital records of VLBWI admitted to a neonatal unit were reviewed for information on patient's body temperature, clinical characteristics and mortality. Comparisons between normothermic and hypothermic VLBWI were performed.

Results Mean gestational age and birth weight of enrolled infants were 29 ± 3 weeks and 1140 ± 253 g, respectively. Prevalence of admission hypothermia was 46.1%, with 38% developing hypothermia within 24-h following admission. VLBWI with hypothermia were more likely to have been born vaginally [aOR 2.85 (1.37–5.91)], have a birth weight < 1000 g [aOR 2.28 (1.25–4.16)], required resuscitation at birth [aOR 2.20 (1.23–3.94)], develop metabolic acidosis [aOR 3.04 (1.35–6.84)] and die within the first week of life [aOR 4.79 (1.43–16.02)].

Conclusions Prevalence of hypothermia in VLBWI is high and is associated with poor outcomes.

Introduction

Very low birth weight infants (VLBWI) have impaired temperature regulatory mechanisms that predispose them to hypothermia. This predisposition is mainly due to high surface-area-to-mass ratio, reduced subcutaneous adipose tissue, a thin stratum corneum and inadequate brown fat [1–3]. Neonatal hypothermia (temperature below 36.5 °C) increases the risk of mortality by 28% for every 1 °C drop in body temperature [4]. Hypothermia also increases the likelihood of developing morbidities like sepsis, metabolic acidosis, respiratory distress, hypoglycaemia and intraventricular haemorrhage (IVH) [5–7].

The prevalence of hypothermia among VLBWI in high-income countries (HIC) ranges from 53.4 to 76.7% [8–11]. There are few studies from low- and middle-income countries (LMIC) that have reported on prevalence of hypothermia on VLBWI despite high burden of preterm births in these countries [12–14]. Hypothermia in VLBWI most likely plays a major role in high neonatal mortality rate observed in LMIC. We therefore determined the prevalence of hypothermia in VLBWI, and assessed the short-term outcomes of hypothermic VLBWI in a neonatal unit in a public tertiary hospital from LMIC.

Patients and study material

Study design and setting

We conducted a retrospective chart review of VLBWI (birth weight < 1500 g) admitted into the neonatal unit at Chris Hani Baragwanath Academic Hospital (CHBAH) from 1 January to 31 December 2016. CHBAH is a public tertiary hospital located in Johannesburg, Gauteng Province in South Africa. The hospital serves as a referral centre for Soweto and surrounding areas with an estimated population of two million people. It caters for ~22,000 live births annually, of which 3–5% are VLBWI. To prevent hypothermia, the neonatal unit protocol requires that all preterm and VLBWI are placed under a radiant warmer soon after birth. Infants born at gestation <30 weeks are placed in a plastic bag without being

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Published online: 30 October 2019

dried, and others are dried under the radiant warmer. All VLBWI have a hat placed on their heads after drying. On admission to the unit, all VLBWI are nursed in an incubator unless they are on mechanical ventilation in which case they are nursed under an overhead radiant warmer. On admission and every 3 h, all neonates have their skin temperature measured and recorded on a temperature chart.

Study population

The study population included VLBWI admitted into the unit between 1 January and 31 December 2016. Infants who were older than 24 h at the time of admission, those without a documented admission temperature, with major congenital anomalies, and those transferred out to other healthcare facilities within the first 7 days of life, were excluded from the study.

Variables

We defined hypothermia as a skin temperature <36.5 °C. Hypothermic infants were sub-classified into mild hypothermia (36.0–36.5 °C), moderate hypothermia (32.0–36.0 °C) and severe hypothermia (<32.0 °C) [1]. Other data collected included gestational age, antenatal steroid exposure (received at least one dose of antenatal steroids), maternal HIV status, birth weight, sex, mode of delivery (vaginal versus caesarean section), place of birth (inborn versus referrals), need for resuscitation and the 5-min Apgar score. Outcome variables assessed were respiratory distress, hypoglycaemia, metabolic acidosis, IVH, sepsis and death within the first 7 days of life. Need for resuscitation was defined as documentation of an infant requiring assistance with breathing using at least bag and mask ventilation. Respiratory distress referred to increased work of breathing demonstrated by the presence of tachypnea (respiratory rate >60), chest retractions, nasal flaring or grunting. Metabolic acidosis was present if the pH was <7.25 and/or the base deficit was more than 10 mmol/L on arterial blood gas analysis. Hypoglycaemia was defined as blood glucose level <2.6 mmol/L. IVH was based on cranial ultrasound findings recorded in the patients' notes by the attending neonatologist. Sepsis was diagnosed if a blood culture grew an organism considered to be a pathogen.

Sample size

We determined the required sample size of 384 using an assumed population prevalence of hypothermia of 62% in VLBWI with a 5% level of precision, a power of 80% and a confidence interval (CI) of 95%. We aimed to collect 480 hospital records of VLBWI to allow for an estimated 30% incomplete data on admission temperature.

Data analysis

Categorical variables were described using frequencies and percentages. Continuous variables were summarised using means with standard deviations or medians with interquartile ranges. In comparing hypothermic and non-hypothermic VLBWI, categorical variables were compared using the chi-squared test or Fisher's exact test, and continuous variables were compared using the Student's t test and Wilcoxon rank-sum test. Multivariate analyses was undertaken using the logistic regression model to identify factors associated with hypothermia or poor outcomes among those with hypothermia. Odds ratio (OR) and 95% CI were computed for all outcomes. All statistical analyses were performed using STATA version 13 (Stata Corp LLC). Statistical significance was defined as two-sided p value < 0.05.

Results

Prevalence of hypothermia among VLBWI

Of the 799 VLBWI admitted to the neonatal unit during the study period, 453 (92.3%) were enrolled into the study (Fig. 1). Forty-six percent ($n = 209$) had hypothermia on admission, of whom 53.1% ($n = 111$), 44.5% ($n = 93$) and 2.4% ($n = 5$) had mild, moderate and severe hypothermia, respectively (Fig. 2). Following admission, 314 infants had temperature records available for the first 24 h of life, with 38% ($n = 120$) of these infants developing hypothermia (Fig. 1).

Characteristics of VLBWI enrolled

Thirty-one percent of sample population ($n = 142$) were HIV exposed, 61% ($n = 257$) received antenatal steroids, 88.7% ($n = 402$) were in-born, 44.6% ($n = 202$) were born by vaginal delivery and 48.6% ($n = 220$) were male (Table 1). The mean (standard deviation) gestational age and birth weight were 29 (±3) weeks and 1140 (±253) grams, respectively. In 15.5% ($n = 64$) of infants, the 5-min Apgar score was <7. Approximately 17% ($n = 79$) of all the infants required resuscitation at birth.

Morbidity and mortality outcomes

Overall, 92.5% ($n = 418$) of the infants had respiratory distress, 27.4% ($n = 124$) had hypoglycaemia, 42.3% ($n = 191$) had metabolic acidosis and 10% ($n = 44$) had sepsis. Of the infants who had a cranial ultrasound done, 17.7% ($n = 41$) had IVH. Ninety-one (20.7%) infants died within the first 7 days of life, and of these deaths, 20.9% ($n = 19$) occurred within the first 24 h of life (Table 1).

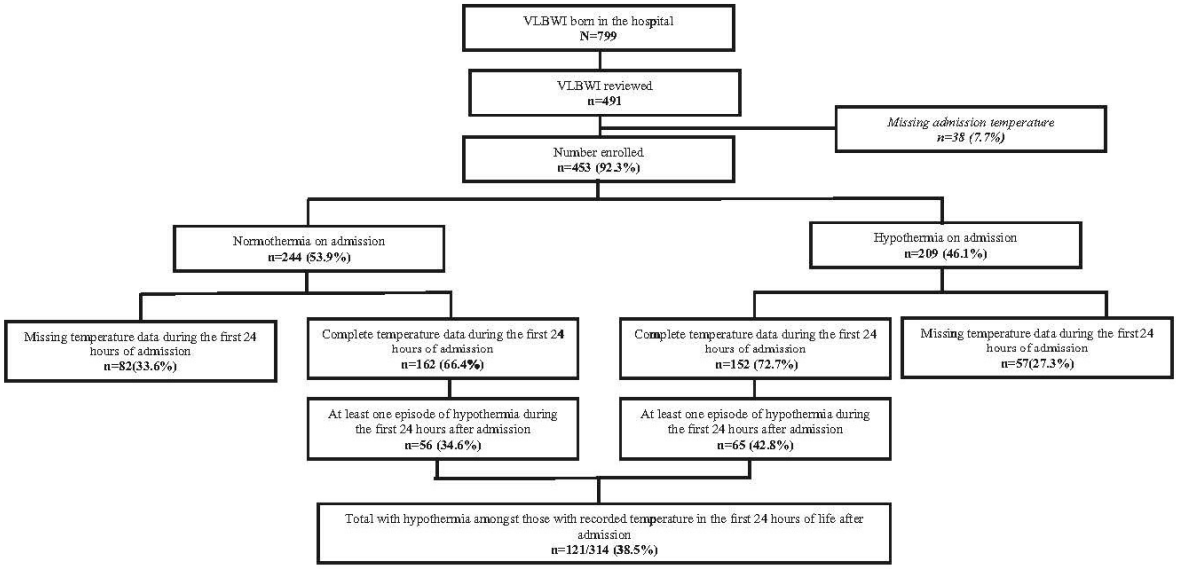

Fig. 1 Hypothermia on admission and within the first 24 h of admission

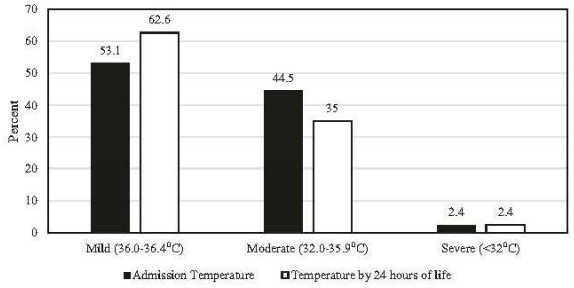

Fig. 2 Categories of severity of hypothermia on admission and at 24 h of life

Hypothermic infants were more likely to develop metabolic acidosis [47.4% versus 37.9%, aOR 3.04 (1.35–6.84)] and to die within the first 7 days of life [24.9% versus 17.2%, aOR 4.79 (1.43–16.02)] (Table 2). Severity of hypothermia did not significantly affect the outcomes of hypothermic infants (Table 3).

Predictors of admission hypothermia in VLBWI

Hypothermic VLBWI were most likely to have been born vaginally [aOR 2.85 (1.37–5.91)], have a birth weight < 1000 g [aOR 2.28 (1.25–4.16)] and have required resuscitation at birth [aOR 2.20 (1.23–3.94)] (Table 4).

Factors associated with mortality in VLBWI

The results of the multivariable analysis are shown in Table 5. Birth weight < 1000 g and resuscitation at birth were significantly associated with mortality [(aOR 15.67 (7.69–31.90) and 4.34 (1.93–9.77)], respectively.

Discussion

We report a high prevalence of hypothermia among VLBWI on admission to the neonatal unit and at 24 h post admission. A significant proportion of VLBWI who had a normal admission temperature developed hypothermia within the neonatal unit. VLBWI with hypothermia were more likely to weigh < 1000 g, be born vaginally, and to require resuscitation at birth. Hypothermia was also associated with the increased risk of mortality in the first week of life.

The prevalence of admission hypothermia among VLBWI (46.1%) reported in this study is lower than previously reported rates of 53–56% from HIC [8, 9], and 62–93% from LMIC countries [10, 11, 13–15]. Our study was comparable with the cited studies on definition of hypothermia, exclusion criteria, mean gestational age and mode of temperature measurement (axillary). However, in our study, delivery room temperature which may have affected the infant's temperature was not recorded. Furthermore, this study used weight instead of gestational age and thus, it is possible that some of the VLBWI were more mature, but growth restricted therefore less risk for hypothermia.

Persistence or development of hypothermia among VLBWI post admission to the neonatal unit is of concern as it suggests sub-optimal thermal care post admission. Most

Table 1 Characteristics of normothermic and hypothermic VLBWI

		All[a] *n/N (%)*	Normothermic *n/N (%)*	Hypothermic *n/N (%)*	Odds ratio (95% CI)
Sex (male)		220/453 (48.6)	117/244 (48.0)	103/209 (49.3)	1.05 (0.73–1.53)
Gestation	(<30 weeks)	251/451 (55.7)	132/244 (54.1)	119/207 (57.5)	1.15 (0.79–1.67)
	Mean ± SD	29 ± 3	29 ± 2	29 ± 3	–
Birth weight	(<1000 g)	133/453 (29.4)	58/244 (23.8)	75/209 (35.9)	**1.79 (1.19–2.70)**
	Mean ± SD	1140 ± 253	1173 ± 233	1102 ± 270	–
Maternal HIV status positive		142/450 (31.6)	75/244 (30.7)	67/206 (32.5)	1.09 (0.73–1.62)
Received antenatal steroids		257/421 (61.0)	143/228 (62.7)	114/193 (59.1)	0.86 (0.58–1.27)
Inborn		402/453 (88.7)	219/244 (89.8)	183/209 (87.6)	1.24 (0.69–2.23)
Vaginal delivery		202/453 (44.6)	98/244 (40.2)	104/209 (49.8)	**1.48 (1.02–2.14)**
Apgar at 5 min <7		64/412 (15.5)	32/225 (14.2)	32/187 (17.1)	1.25 (0.73–2.12)
Required resuscitation at birth		79/452 (17.5)	29/243 (11.9)	50/209 (23.9)	**2.32 (1.41–3.83)**

[a]Missing values for maternal HIV status ($n = 3$), antenatal steroids ($n = 32$), Apgar at 5 min ($n = 41$), gestational age ($n = 2$)

Bold values indicate statistical significance odds ratio results

Table 2 Outcomes associated with admission hypothermia

	All[a] *n/N (%)*	Normothermic *n/N (%)*	Hypothermic *n/N (%)*	OR (95% CI)	aOR (95% CI)
Respiratory distress	418/452 (92.5)	224/243 (92.2)	194/209 (92.8)	1.09 (0.54–2.22)	–
Hypoglycemia	124/452 (27.4)	69/243 (28.4)	55/209 (26.3)	0.90 (0.59–1.36)	–
Metabolic acidosis	191/452 (42.3)	92/243 (37.9)	99/209 (47.4)	**1.48 (1.01–2.15)**	**3.04 (1.35–6.84)**[b]
Intraventricular haemorrhage	41/231 (17.7)	24/122 (19.7)	17/109 (15.6)	0.69 (0.37–1.30)	–
Sepsis	44/439 (10)	24/238 (10.1)	20/201 (10)	1.03 (0.56–1.91)	–
Death	91/439 (20.7)	41/238 (17.2)	50/201 (24.9)	**1.59 (1.00–2.53)**	**4.79 (1.43–16.02)**[b]

OR odd ratio, *aOR* adjusted odds ratio

[a]Missing values: respiratory distress ($n = 1$) hypoglycaemia ($n = 1$) metabolic acidosis ($n = 1$) IVH ($n = 204$), sepsis ($n = 14$), death ($n = 14$)

[b]Adjusted for mode of delivery, birth weight, resuscitation at birth

Table 3 Prevalence of adverse events in VLBWI according to severity of hypothermia

	All Hypothermic[a] *n/N (%)*	Mild hypothermic *n/N (%)*	Moderate to severe hypothermic *n/N (%)*	OR (95% CI)
Respiratory distress	194/209 (92.8)	100/111 (90.1)	94/98 (95.9)	2.59 (0.80–8.40)
Hypoglycemia	55/209 (26.3)	32/111 (28.8)	23/98 (23.5)	0.76 (0.41–1.41)
Metabolic acidosis	99/209 (47.4)	47/111 (42.3)	52/98 (53.1)	1.54 (0.89–2.66)
Intraventricular haemorrhage	17/109 (15.6)	8/59 (13.6)	9/50 (18.0)	1.40 (0.50–3.95)
Sepsis	20/201 (10)	11/109 (10.1)	9/92 (9.8)	0.97 (0.38–2.44)
Death	50/201 (24.9)	21/109 (19.3)	29/92 (31.5)	1.93 (1.01–3.69)

OR odds ratio

[a]Missing values: IVH ($n = 100$), sepsis ($n = 8$), death ($n = 8$)

VLBWI in the unit are nursed in an incubator, and the high incidence of hypothermia post admission implies incubators were inadequate source of heat, either from their incorrect use or their malfunctioning. Incubators have been reported to be less effective in maintaining body temperature in neonates when compared with kangaroo mother care (KMC) [16].

Contrary to other studies, in this study we found that vaginal deliveries were more likely to be hypothermic on admission. The higher rate of hypothermia observed with vaginal compared with caesarean section delivery in this study is most likely due to differences in environmental temperatures. Delivery ward in this study setting is an open hall with cubicles closed with hanging curtains. This design makes it difficult to maintain labour and delivery room temperatures within the recommended temperatures of 25–27 °C. Due to a limited number of personnel in our institution, fewer number of vaginal deliveries are attended by a healthcare provider whose sole responsibility is to look after the new born baby compared to those born by caesarean section. An infant receiving 100% attention from the healthcare provider after delivery is most likely to receive better thermal care. This finding highlights the importance of having a healthcare provider dedicated to the care of infant at the time of delivery.

The association observed between hypothermia and need for resuscitation is most likely due to infants who required resuscitation having been exposed to the cold environment for longer periods with inadequate temperature control measures during resuscitation.

We found a significant association between hypothermia and presence of metabolic acidosis, and between hypothermia and high mortality. Hypothermia may cause peripheral vasoconstriction and increase oxygen demand leading to anaerobic metabolism with subsequent development of metabolic acidosis [2, 5]. These findings also support previous studies that admission hypothermia is associated with increased risk for mortality [8–10].

Findings from this study highlight the need for more emphasis being placed in thermal care in the first 24 h of life. One such approach involves adopting a 'thermoregulatory bundle' that includes maintenance of appropriate ambient temperature between 24 and 27 °C in labour and delivery room, training of all midwives in practices of maintaining normal temperature and prevention of heat loss immediately after birth especially during resuscitation [17]. A temperature bundle that includes maintenance of labour and delivery room temperature, wrapping VLBWI in

Table 4 Predictors of admission hypothermia among VLBWI

	OR (95% CI)	aOR (95% CI)
Mode of delivery (vaginal)	1.48 (1.02–2.14)	2.85 (1.37–5.91)[a]
Birth weight (<1000 g)	1.79 (1.19–2.70)	2.28 (1.25–4.16)[b]
Resuscitation at birth	2.32 (1.41–3.83)	2.20 (1.23–3.94)[c]

OR odds ratio, *aOR* adjusted odds ratio, *CI* confidence interval

[a]Adjusted for birth weight, resuscitation at birth

[b]Adjusted for mode of delivery, resuscitation at birth

[c]Adjusted for birth weight, mode of delivery

Table 5 Factors associated with mortality in VLBWI

	All[a] *n/N* (%)	Survived *n/N* (%)	Died *n/N* (%)	OR (95% CI)	aOR (95% CI)
Maternal HIV status (positive)	138/436 (31.7)	105/347 (30.3)	33/89 (37.1)	1.36 (0.83–2.21)	–
Received antenatal steroids	253/408 (62.0)	216/324 (66.7)	37/84 (44.0)	**0.39 (0.24–0.64)**	0.54 (0.26–1.14)
Inborn	389/439 (88.6)	310/349 (89.1)	79/91 (86.8)	1.24 (0.62–2.48)	–
Vagina delivery	193/439 (44.0)	132/348 (37.9)	61/91 (67.0)	**3.33 (2.04–5.42)**	1.25 (0.59–2.64)
Sex (male)	214/439 (49.0)	169/348 (48.6)	45/91 (49.5)	1.04 (0.65–1.64)	–
Birth weight (<1000 g)	125/439 (28.5)	55/348 (15.8)	70/91 (76.9)	**17.76 (10.1–31.3)**	**15.67 (7.69–31.90)**
Apgar at 5 min (<7)	59/398 (14.8)	37/325 (11.4)	22/73 (30.1)	**3.36 (1.83–6.15)**	1.06 (0.46–2.46)
Hypothermia at admission	201/439 (45.8)	151/348 (43.4)	50/91 (54.9)	**1.59 (1.00–2.53)**	0.94 (0.48–1.84)
Respiratory distress	407/439 (92.7)	318/348 (91.4)	89/91 (97.8)	4.20 (0.98–17.1)	–
Hypoglycemia	120/439 (27.3)	102/348 (29.3)	18/91 (19.8)	0.59 (0.34–1.05)	–
Metabolic acidosis	186/439 (42.4)	144/348 (41.4)	42/91 (46.2)	1.21 (0.76–1.93)	–
IVH	41/231 (17.8)	25/188 (13.3)	16/43 (37.2)	**2.79 (1.38–5.62)**	–
Sepsis	45/439 (10.3)	40/348 (11.5)	5/91 (5.5)	0.45 (017–1.17)	–
Required resuscitation at birth	74/439 (16.9)	37/348 (10.6)	37/91 (40.7)	**5.76 (3.36–9.88)**	**4.34 (1.93–9.77)**

[a]Missing values: maternal HIV status ($n = 3$) *antenatal steroids ($n = 31$) gestation ($n = 2$) *Apgar at 5 min ($n = 41$) IVH ($n = 208$)

OR odds ratio, *aOR* adjusted odds ratio

polyethylene bags and putting on cotton caps can also be adopted as it has been shown to reduce incidence of admission hypothermia by 62% [17]. To prevent hypothermia post admission to the neonatal unit, appropriate use of incubators and overhead radiant warmers, avoiding unnecessary exposure of VLBWI, and early use of KMC can be adopted.

Limitation in this study is related to inherent flaws of a retrospective design. Missing data resulting in exclusion of some infants, and non-random selection (first records to be retrieved were used) might have increased the risk of selection bias. It is therefore possible that the sample is not representative of the general population limiting generalisability of this study's findings. In addition, there was no data on adherence to standards of care to prevent hypothermia, which made it difficult to evaluate the impact of (non) adherence to the standards on the level of hypothermia among the VLBWI. Despite these limitations, the study was adequately powered to detect significant occurrence of hypothermia on admission.

Conclusion

Hypothermia among VLBWI is a significant problem that is associated with adverse outcomes. Quality improvement initiatives focussing on prevention of neonatal hypothermia should be implemented in neonatal units. The initiatives should address malfunctioning equipment and advocate for KMC as part of thermoregulatory bundle in the care of VLBWI.

Acknowledgements We acknowledge the work done by the clinical staff at the Chris Hani Baragwanath Academic Hospital neonatal unit, and the records department for assistance in retrieval of the medical records.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Ethical statement Ethical approval for the study was received from the University of Witwatersrand Human Research Ethics Committee prior to undertaking the study (Protocol reference number M170540).

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APPENDICES

Appendix 1: Approved research protocol

HYPOTHERMIA AMONG NEONATES ADMITTED TO THE NEONATAL UNIT AT A TEACHING HOSPITAL IN SOUTH AFRICA

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INTRODUCTION

Background

The global under-5 child mortality rate has progressively and consistently decreased during the last three decades, from 110 per 1,000 in 1980 to 60 per 1,000 in 2009. Accordingly, the number of child deaths worldwide each year has decreased from 13.5 million in 1980 to 2.7 million neonatal deaths in 2015. Although the number of neonatal deaths has also decreased, from 5.1 million deaths annually in 1990 to approximately 2.7 million in 2015, the decline in neonatal mortality has been slower than the decline in the post-neonatal (1-59 months) mortality rate. Therefore, neonatal deaths currently represent a larger share of the total under-five deaths. In 2013, about 44 per cent of all under-five deaths occur in the first 28 days of life, which is an increase from 37 per cent in 1990.(1)

Neonatal deaths are not equally distributed around the globe, and more than 99% of all deaths occur in developing countries. As a region, Sub-Saharan Africa is estimated to have a neonatal mortality rate of 29 per 1000 live births, compared with 4 per 1,000 in high-income countries. (1,2). Neonatal mortality rate in South Africa is estimated to be at 11 per 1000 live births(1).

Temperature regulation is a critical function in the neonate, with hypothermia being an important determinant of the neonatal survival. Newborns achieve temperature regulation through mechanisms controlled by the hypothalamus and mediated by endocrine pathways through shivering and non-shivering thermogenesis (3). However, these thermoregulatory mechanisms are easily overwhelmed, especially in premature and low birth weight infants resulting in hypothermia. The World Health Organisation (WHO) has classified the severity of hypothermia as: cold stress or mild hypothermia = 36.0–36.4°C; moderate hypothermia = 32.0–35.9°C; and severe hypothermia = < 32°C (14), and the severity of complications depends on the degree of hypothermia. Studies have further shown that a single episode of hypothermia increases the likelihood of neonatal death by 28% (4). Some implementation studies have demonstrated that interventions aimed at reducing hypothermia result in a 18-42% decrease in neonatal mortality and morbidity(5).

Newborn hypothermia is ubiquitous, although the incidence of hypothermia varies from country to country. Overall in community-based studies (all conducted in Nepal or India), hypothermia prevalence ranges from 11% to 92% (6). The exact incidence of neonatal hypothermia in sub- Saharan Africa is unknown due to paucity of community based studies on the subject matter. However, hospital-based studies on neonatal hypothermia suggest a high prevalence but with a great inter-Country variations. In Nigeria, a cross sectional study

conducted among 150 babies at point of admission reported a prevalence rate of 62% (7). In Guinea-Bissau, a temperature evaluation of 2926 babies within 12 hours of birth found 8.1% of the babies had temperatures below 34.5°C (8). In East Africa, the incidence of neonatal hypothermia was varied, with rates ranging from 22.4% in a Tanzanian study(9) to 27.2% in a Kenyan study (10).

A combination of environmental factors, cultural practices, and socioeconomic factors predispose a newly born infant to hypothermia. Low birthweight is a major risk factor for neonatal hypothermia. This is because of a number of physical as well as physiologic reasons: They have a high surface-area-to-mass ratio which increases evaporative heat loss; they have insufficient amounts of subcutaneous adipose tissue which reduces the skin's insulation ability; Neonates have an immature epidermis that has little stratum corneum. This increases evaporative loss through increased trans- epidermal water loss; they have limited stores of brown fat (especially early premature neonates) therefore unable to generate heat through non-shivering thermogenesis. (11–14). Other highly prevalent host factors that might have contributed to the burden of hypothermia in sub- Saharan Africa include perinatal asphyxia,(15) neonatal hypoglycaemia and neonatal infections (16). Unlike the small-for-gestational age and preterm babies who do not have adequate store of brown fat for thermogenesis, the hypoglycaemic and asphyxiated babies do not have the necessary fuel to generate the brown fat oxidation. In some studies, infants with low Apgar score, infants born from multiple pregnancies and infants who received CPR had higher risk of being hypothermic (17).

Hypothermia is one the most important cause of neonatal morbidity. Hypothermic neonates undergo a number of adaptive physiologic changes which may be life threatening. Hypothermia causes peripheral vasoconstriction which may lead to tissue hypoxia and subsequently to metabolic acidosis (18). Hypothermic infants additionally have increased cellular metabolism that results in increased oxygen and glucose requirements. This may lead to respiratory distress(19) and hypoglycaemia (20) Finally, hypothermia may result in pulmonary vasoconstriction which may delay successful transition to extra uterine life (21). If hypothermia is left untreated there is risk of neurological complications, including intraventricular haemorrhage (22).

In South Africa, the incidence of, and outcomes of VLBW infants admitted with hypothermia have not yet been studied. Therefore, this study proposes to determine the incidence of hypothermia, as well as describe the outcomes among VLBW infants admitted to the neonatal unit of the Chris Hani Baragwanath Hospital.

Study Justification

Hypothermia is an important determinant of neonatal mortality. The incidence of hypothermia and outcomes of babies with hypothermia on admission to neonatal units in South African hospitals is lacking. Moreover, existing studies on neonatal hypothermia have focused on incidence and prevalence rates. This study will therefore add to the growing body of knowledge on hypothermia, with a view of informing policy development on more practical interventions that may reduce the incidence of hypothermia among admitted neonates.

STUDY OJECTIVES

Broad Objective

The broad objective of the study is to determine the incidence and evaluate the effects of admission hypothermia on short- term outcomes of hypothermia among neonates admitted to the neonatal unit of the Chris Hani Baragwanath Hospital.

Specific Objectives

i. To determine the incidence of hypothermia among Very Low Birth Weight (VLBW) infants within the first 24 hours of life.
ii. To describe the characteristics of VLBW infants found to be hypothermic.
iii. To determine short term outcomes in VLBW infants found to be hypothermic.
iv. To determine the predictors of hypothermia among VLBW infants admitted at the neonatal unit.

STUDY METHODOLOGY

Study Design

The study will be a retrospective cohort study.

Sample Size

The formula to be used to calculate sample size will be as described in Kelsey et.al (23)

Kelsey et al., Methods in Observational Epidemiology 2nd Edition, Table 12-15
Fleiss, Statistical Methods for Rates and Proportions, formulas 3.18 &3.19

CC = continuity correction

The sample size formula for the method described in Kelsey et. al. is:

$$n_1 = \frac{\left(Z_{\alpha/2} + Z_{1-\beta}\right)^2 \bar{p}\bar{q}(r+1)}{r(p_1 - p_2)^2}$$

and

$$n_2 = r\,n_1$$

where

n_1 = number of exposed

n_2 = number of unexposed

$Z_{\alpha/2}$ = standard normal deviate for two-tailed test based on alpha level (relates to the confidence interval level)

Z_{β} = standard normal deviate for one-tailed test based on beta level (relates to the power level)

r = ratio of unexposed to exposed

p_1 = proportion of exposed with disease and $q_1 = 1-p_1$

p_2 = proportion of unexposed with disease and $q_2 = 1-p_2$

$$\bar{p} = \frac{p_1 + rp_2}{r+1} \quad \text{and} \quad \bar{q} = 1 - \bar{p}$$

The calculated sample size for the study will be 328

Study Setting

The study will be conducted at the Neonatal unit of Chris Hani Baragwanath Hospital, a teaching and referral hospital of the University of Witwatersrand. The hospital is located in Johannesburg, Gauteng Province, South Africa.

The hospital's neonatal unit comprises of 4 distinct sub units: Labour ward nursery, High Care ward (Transitional ICU-TICU), Neonatal ICU, Long stay wards (ward 66, ward 40). The neonatal unit admits approximately 500 neonates every month with majority of the admissions being from the hospital's maternity unit.

Study Period

Data will be collected on patients admitted to the neonatal unit from June 2016 to December 2016

Study Population

Inclusion criteria

At risk neonates admitted to the neonatal unit of Chris Hani Baragwanath hospital. At risk neonates will be defined as those who are classified as being Very Low Birth Weight (VLBW).

Exclusion criteria

Neonates with the following characteristics will be excluded from the study:

- Age at time of admission >24 hours old
- Neonates whose admission files have no temperature records for the first 24 hours of life.
- Neonates with a birth weight >1500 g or birth weight<750g
- Neonates with significant congenital anomalies especially abdominal wall defects

Study Variables

Independent variables

- Admission temperature

Dependent variables

- **Demographic characteristics**
  - Gestational age
  - Sex of the baby
  - Birth weight
- **Clinical characteristics:**
  - Mode of delivery (vaginal Vs caesarean section)
  - Site of delivery(in born vs referral)
  - Age (hours) at admission
  - APGAR
  - Delivery room resuscitation
- **Outcome variables:**
  - Hypoglycaemia
  - Metabolic acidosis
  - Respiratory distress

- Intra-ventricular haemorrhage
- Mortality

Study Procedures

Data collection

Files for neonates who were admitted during the study period will be retrieved from the records department. Those patients who do not have any of the exclusion criteria will be recruited into the study. Temperature on admission to the neonatal unit will be collected. This data will be extracted from individual patient files. Patients with a documented temperature below 36.5^0 centigrade will be classified as being hypothermic.

Additional data to be extracted from patient records will include the following: Gestational age; Birth weight; Sex; Mode of delivery; Place of birth (in-born or referral from another facility); the age (in hours) at admission

Study Outcomes

These will be classified as being either a primary outcome or a short term secondary outcomes

- Primary outcome: Normothermia vs Hypothermia
- Short term secondary outcomes will include the following: Respiratory distress; Metabolic acidosis; Hypoglycaemia; Intraventricular haemorrhage; Mortality

Operational Definitions

- *Hypothermia*: Body temperature below 36.5° C (14)
- *Normothermia*: Body temperature between 36.5° and 37.5° C (14)
- *Short term secondary outcomes*: Morbidity and mortality variables occurring within the first 72 hours of life. These will be assessed at 2 different time periods: Before 24 hours of life and at 72 hours of life
- *Respiratory distress*: Increased work of breathing demonstrated by the presence of one or more of the following: tachypnea (respiratory rate>60), chest retractions, nasal flaring, grunting (24)
- *Metabolic acidosis*: Defined as pH < 7.20 and/or base deficit > 10 mmol/L
- *Hypoglycaemia*: Defined as blood glucose level less than 3.3mmol/L (25)
- *Intraventricular haemorrhage*: Defined according to the Papile et al classification (26)
- *Mortality*: death within the first 72 hours

- Delivery room resuscitation- Chest compressions with or without administration of medications.

Data Analysis

Categorical data will be analysed using the standard $\chi 2$ test and Fisher's exact test (non-parametric). Continuous data will be analysed using the independent t-test and the nonparametric Wilcoxon rank-sum test for between-group comparisons, where appropriate. Multivariate analyses will be performed using the logistic regression model to identify the implications of hypothermia with respect to short-term outcomes. Demographic and clinical variables including gestational age, resuscitation, and sex, will be included in the logistic regression models to identify the variables significantly associated with these outcomes. Adjusted odds ratios (ORs) and 95% confidence intervals (CIs) will be computed for all outcomes. All statistical analyses will be performed using SPSS version 23. Statistical significance will be defined as $P < .05$. All P values in this analysis will be of the 2-sided type.

ETHICAL CONSIDERATIONS

Ethical approval will be obtained from the University of the Witwatersrand Protocol Review Committee and Human Research Ethics Committee (HREC) prior to undertaking the study. Because only retrospective data will be collected and data collection tools will contain unique study identifiers and not patient names, there will be no need to obtain consent from individual patients.

STUDY LIMITATIONS

The study is a retrospective analysis of existing patient records therefore some records may not be complete

TIME LINES

	Oct 2016	**Nov 2016**	**Dec 2016**	**Jan 2017**	**Feb 2017**	**Mar 2017**	**Apr 2017**	**May 2017**	**June 2017**	**July 2017**	**Aug 2017**		
Literature review													
Protocol preparation													
Protocol assessment													

Ethics application													
Data collection													
Data analysis													
Write-up report													
Write-up paper													

FUNDING

Cost of funding will be borne by the study investigator. The Estimated budget is expected to be R 7,500.

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Appendix 2: Ethics clearance

R14/49 Dr Jacqueline Ng'eny

HUMAN RESEARCH ETHICS COMMITTEE (MEDICAL)

CLEARANCE CERTIFICATE NO. M170540

NAME: (Principal Investigator)	Dr Jacqueline Ng'eny
DEPARTMENT:	Paediatrics Chris Hani Baragwanath Academic Hospital
PROJECT TITLE:	Hypothermia among Neonates Admitted to the Neonatal Unit at a Teaching Hospital in South Africa
DATE CONSIDERED:	26/05/2017
DECISION:	Approved unconditionally
CONDITIONS:	
SUPERVISOR:	Prof Sithembiso Velaphi

APPROVED BY: Prof P Cleaton-Jones, Chairperson, HREC (Medical)

DATE OF APPROVAL: 28/06/2017

This clearance certificate is valid for 5 years from date of approval. Extension may be applied for.

DECLARATION OF INVESTIGATORS

To be completed in duplicate and **ONE COPY** returned to the Research Office Secretary in Room 301, Third floor, Faculty of Health Sciences, Phillip Tobias Building, 29 Princess of Wales Terrace, Parktown, 2193, University of the Witwatersrand. I/we fully understand the conditions under which I am/we are authorized to carry out the above-mentioned research and I/we undertake to ensure compliance with these conditions. Should any departure be contemplated, from the research protocol as approved, I/we undertake to resubmit the application to the Committee. **I agree to submit a yearly progress report**. The date for annual re-certification will be one year after the date of convened meeting where the study was initially reviewed. In this case, the study was initially reviewed in May and will therefore be due in the month of May each year. Unreported changes to the application may invalidate the clearance given by the HREC (Medical).

Principal Investigator Signature _____ Date _____

PLEASE QUOTE THE PROTOCOL NUMBER IN ALL ENQUIRIES

Appendix 3: Turnitin report

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ORIGINALITY REPORT

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