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Hypothermia in Preterm Newborns: Impact on Survival

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Abstract

Background. Globally, prematurity is the leading cause of neonatal mortality, and hypothermia is one of its contributing factors. The goal of this study was to determine the association between hypothermia and mortality. *Methods.* A prospective, multi-center, descriptive clinical study was conducted in 5 hospitals in Ethiopia. Axillary temperatures were taken at the time of admission to the newborn intensive care units (NICU) and followed during the NICU stay. *Results.* A total of 3852 premature neonates (<37 weeks) were admitted to the NICUs from July 2016 to May 2018. Of these infants, 1109 (28.8%) died and 2991 (79.6%) had hypothermia. Hypothermia was associated with perinatal asphyxia (89.5%), RDS (86.2%), and resuscitation at birth (82.7%). Admission temperatures in preterm newborns were inversely associated with mortality and morbidity. *Conclusion.* Hypothermia at admission is associated with neonatal mortality in premature neonates in Ethiopia. RDS and perinatal asphyxia were the main factors associated with hypothermia. The very high prevalence and association with mortality warrants quality improvement interventions.

Keywords

Hypothermia, Neonatal mortality, prematurity, Neonatal Intensive Care Units, LMIC

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Introduction

Worldwide, about 2.5 million newborns die every year in the first 4 weeks of life.[1] Most neonatal deaths (99%) occur in low and middle-income countries (LMICs) and about half of the deaths occur at home.[1] Prematurity is the most common cause of neonatal deaths. The overall estimated preterm birth rate is 11.1%, and around 60% of preterm births world-wide occur in sub-Saharan Africa and south Asia. Ethiopia has an estimated preterm birth rate of 14.1 per 1000 live births and belongs to the top 15 countries that contribute 40% to 60% of neonatal deaths.[2] An 8-year survey reported that 67% of high-risk and LBW infants were hypothermic on admission,[2] which makes it a significant global health issue, although it may be difficult to fully determine its specific contribution to neonatal mortality.

Neonatal hypothermia has been considered a contributing cause of mortality and morbidity among both low-birth weight and normal weight babies, even in warm tropical environments. Hypothermia was associated with hypoglycemia, metabolic acidosis, hypoxia, respiratory

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distress syndrome (RDS), chronic lung disease, coagulation defects, intraventricular hemorrhage, sepsis and increased insensible water loss leading to dehydration, fluid and electrolyte imbalance, and hypotension.[3-5] Particularly severe categories of hypothermia were also associated with high mortality.[5] The World Health Organization (WHO) recommends a broad classification of hypothermia with mild (36.0°C-36.4°C), moderate (35.9°C-32.0°C) and severe (<32.0°C) categories[6,7]; however, Sodemann et al suggest that the current "moderate" category is too wide (32.0°C-35.9°C) because it is related to very different outcomes. Therefore, they recommended shifting the "severe" category to <34.0°C (Grade 4).[8] This new classification system better reflects subsequent mortality risk across the range of observed temperatures, increases the awareness of hypothermia by expanding the most severe category, and allows taking a better approach for appropriate actions.[8,9]

Hospital-based studies have reported increased mortality with admission temperatures <36.5°C,[10] but the relationship between severity and duration of hypothermia and death has been reported less frequently and reports on hypothermia mostly lack adjustment for gestational age (GA) or birthweight.[10]

This paper attempts to determine the magnitude of hypothermia and its association with poor neonatal outcomes in newborn intensive care units (NICU) in Ethiopia.

Methods

This analysis uses data from a prospective, multi-center, descriptive clinical study of preterm neonates.[11,12] The study was conducted in 5 hospitals in 3 regions of Ethiopia, including Addis Ababa (St Paul Millennium College Hospital, Tikur Anbessa Hospital, and Gandhi Memorial Hospital), Gondar, north-western Ethiopia (Gondar University Hospital), and Jimma, south-western Ethiopia (Jimma University Hospital).

All live-born preterm infants <7 days of life without major malformations, either born in or transferred to these hospitals during the study period were eligible. Algorithms were developed to decide "best gestational age" to document whether the infant met the inclusion criterion of "preterm" that is, <37 weeks gestation at delivery. A hierarchy of criteria was used from most preferred method to least preferred method that is, ultrasound at ≤28 weeks of gestation when available was the most preferred method followed by ultrasound at >28 weeks and either mother's report of last menstrual period (LMP) or New Ballard scores. If there is no ultrasound, LMP when judged reliable and New Ballard scores when other criteria were not available were used.[11]

If the temperature at admission to the NICU was recorded, neonates were included for this analysis. Many late preterm newborns were discharged directly home and were never admitted into a NICU. Axillary temperature was taken using digital thermometers and measured in degrees Celsius. Admission temperature was the first measurement taken at admission to the NICU.

All admitted infants had body temperatures taken at least twice daily and/or more frequently when required in critically sick babies. The NICU nurses were trained to follow a standardized protocol to take temperature measurement and document the findings on standard case report forms (CRFs). The site coordinator and the nurse coordinators insured that all forms were completed. All NICUs had incubators to keep the preterm infants warm and the rooms were kept warm using radiant heaters, even though we did not measure the ambient temperature of each NICU throughout the study period.

Operational Definitions

Admission temperature: the first temperature taken after the newborn was admitted to the NICU.

High temperature or fever: Axillary temperature above 37.5°C

Low temperature or hypothermia: Axillary temperature less than 36.5°C

Normal temperature or normothermia: Axillary temperature 36.5°C to 37.5°C

Persistent hypothermia: If the axillary temperature was still below 36.5°C for more than 12 hours after admission to the NICU.

Inborn: Newborn delivered in the same hospital.

Out born: Newborn delivered outside the hospital and transferred to admitting NICU.

Data Collection and Analysis

Obstetric and neonatal factors including gestational age, birth weight of the infant, mode of delivery, place of delivery, whether the birth was single or multiple, resuscitation at birth, and neonatal conditions such as asphyxia, sepsis, and RDS were recorded. Data were transferred on a weekly basis from each participating study hospital to a central data management unit at Addis Ababa University, creating a merged data repository. Descriptive statistics were performed using Stata version 14.2 (2017 package). The associations of pregnancy, delivery, and neonatal variables were compared to admission hypothermia including different levels of hypothermia in ranges of Celsius degrees 36.0 to 36.4; 35.0 to 35.9, 34.0 to 34.9, 33.0 to 33.9, 32.0 to 32.9, and <32.0. Temperatures greater 37.5°C were considered

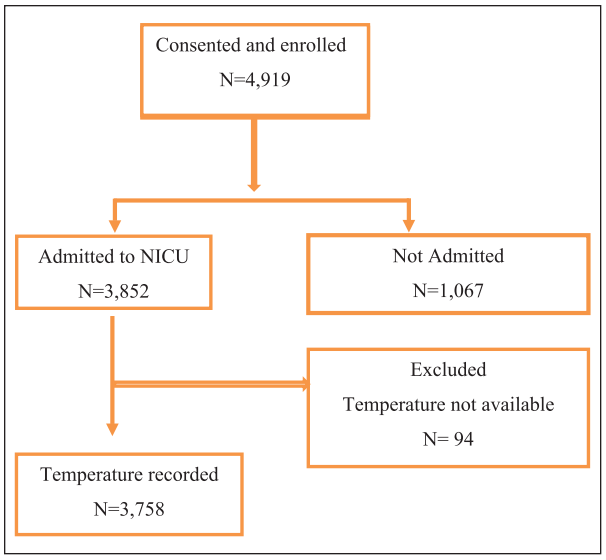

Figure 1. Enrollment flow diagram.

elevated. Infants with an admission temperature of 36.5°C to 37.5°C (ie, the normal range) were considered the control group.

Ethical Approval and Informed Consent

All clinical procedures were conducted per hospital protocol. The study was approved by the Institutional Review Boards of each hospital and the College of Health Sciences of the Addis Ababa University (IRB approval number: AAUMF 03-008). Informed and written consent was obtained from parents or caretakers prior to the infants' participation in the study. Consent information was available in English, Amharic or Oromifa languages, as appropriate. Confidentiality of the information was maintained.

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Results

Over a period of nearly 2 years, from July 2016 to May 2018, a total of 4919 preterm infants were enrolled into the main study, of which 3852 were admitted to a NICU (Figure 1). A total of 3758 of the enrolled infants had documented admission temperatures. Of the 3758 with recorded temperatures, 2991 (79.5%) had admission hypothermia (temperature less than 36.5°C). Of the 3852 infants admitted to the NICU, 1109 died (28.8%).

Of the 3758 preterm neonates with measured temperature, 710 (18.9%) had normal temperatures at admission, 57 (1.6%) had high temperatures, and the remaining 2991 (79.6%) had hypothermia (Table 1). Of all admissions with a temperature recorded, 16.0% had temperatures between 36.0°C and 36.4°C, 27.2% had temperatures between 35.0°C and 35.9°C, 22.6% had temperatures between 34.0°C and 34.9°C and 9.1% had temperatures 33.0°C to 33.9°C. Almost half of all admitted infants (N = 1871; 49.7%) had temperatures between 34.0°C and 35.9°C). Only 5 infants had temperatures less than 32.0°C (0.2%) and because of the small number, they were added to the <33°C group.

Table 1 depicts details of the association between admission temperature and mortality. Infants in all groups with a temperature less than 36.5°C had significantly increased mortality. Mortality increased with decreasing admission temperature from 19.2% with a normal temperature to 62.8% with a temperature of <−33°C (OR 7.1). Preterm neonates with temperatures of more than 37.5°C had a higher mortality than the infants with normal temperatures (28.1% vs 19.2%), but the difference was not statistically significant ($P = .107$).

Table 2 depicts the associations of perinatal conditions with hypothermia <36.5°C: perinatal asphyxia (OR 2.6, 95% CI: 1.6-4.5, $P < .000$), RDS (OR 2.2, 95% CI: 1.7-2.5, $P < 0.000$). Resuscitation at birth was significantly associated with hypothermia (OR 1.3, 95% CI: 1.0-1.7, $P = .046$). Sepsis was negatively associated with hypothermia (OR 0.8, 95% CI: 0.6-0.9, $P < .001$). Caesarean delivery, the use of corticosteroids and multiple births were not significantly associated with hypothermia.

Table 3 presents the proportion of deaths in hypothermic preterm neonates compared to normothermic preterm neonates by gestational age and birth weight categories. It describes the association of mortality to admission hypothermia by gestational age and birth weight categories. There were no differences in mortality rates between the hypothermic and normothermic infants in the GA groups <28 weeks or 35 to 36 weeks; however, there were significantly higher mortality rates among the hypothermic infants compared to the normothermic infants in the GA groups of 28 to 31 and 32 to 34 weeks with ORs of 2.04 and 1.43, respectively. There was a statistically significant difference in mortality in all birthweight categories except for those infants above 2000 g.

Table 4 compares the admission temperature with the temperature recorded after 12 hours of stay in the NICUs. Among the 2991 hypothermic preterm newborns, 55% were hypothermic after 12 hours of NICU stay. Among the 701 infants with normal temperature and among the 57 infants who had hyperthermia at admission, 30% and 27%, respectively developed hypothermia.

Table 1. Admission Body Temperature and Mortality.

Temperature in °C	No. of newborns (%)	No. died	% Died	OR (95% CI)	*P* value
>37.5	57 (1.5%)	16	28.1	1.6 (0.90, 3.02)	.107
36.5-37.5	710 (18.9%)	136	19.2	Reference group	
36.0-36.4	603 (16.0%)	144	23.9	1.3 (0.96, 1.61)	.038
35.0-35.9	1023 (27.2%)	278	27.2	1.6 (1.25, 1.99)	.000
34.0-34.9	848 (22.6%)	270	31.9	2.0 (1.56, 2.50)	.000
33.0-33.9	345 (9.2%)	139	40.3	2.9 (2.14, 3.79)	.000
<33	172 (4.58%)	108	62.8	7.1 (4.96, 10.22)	.000
Total	3758	1091	29.0		

Table 2. Association of Risk Factors With Hypothermia.

Risk factor	Categories	N	Percent hypothermia	OR	95% CI	*P* value
Out born	Yes	616	83.6	1.25	[0.992, 1.575]	.059
	No	3043	80.3			
Sepsis	Yes	1367	78.2	0.77	[0.652, 0.909]	.002
	No	2332	82.3			
Asphyxia	Yes	251	91.2	2.60	[1.662, 4.051]	.000
	No	3448	80.1			
RDS	Yes	1680	87.0	2.16	[1.814, 2.574]	.000
	No	2019	75.6			
Resuscitation at birth	Yes	532	84.2	1.29	[1.005, 1.658]	.046
	No	2879	80.5			
Caesarian delivery	Yes	1409	80.3	0.95	[0.805, 1.127]	.570
	No	2254	81.1			
Maternal steroids given	Yes	1062	79.2	0.87	[0.724, 1.035]	.114
	No	2541	81.5			
Multiple Birth	Yes	1246	81.0	1.02	[0.854, 1.208]	.857
	No	2455	80.7			

Discussion

Our study on hypothermia in Ethiopian NICUs, demonstrated that nearly 80% of preterm neonates were hypothermic at admission. Lower gestational age and lower birth weight were associated with a higher rate and more severe hypothermia. Mortality was significantly associated with lower body temperatures with a clear dose-response relationship. Our study showed that asphyxia, RDS, and resuscitation at birth were risk factors significantly associated with hypothermia.

A small study of 88 cases from northern Ethiopia reported that preterm babies had a 3.6 times higher risk of hypothermia than term infants[13] and several large studies reported up to 5 times higher hypothermia rates in preterm compared to term neonates in Ethiopia, Guinea-Bissau, and Nepal.[8,14-16] These findings stress the importance of specifically targeting preterm neonates for corrective interventions related to hypothermia in the NICU.

The high rate of hypothermia in the present study specifically targeting preterm neonates found an even larger prevalence of hypothermia than the earlier reported 64% from a smaller, 1-month study of 356 preterm neonates in Addis Ababa.[14] The rates of hypothermia and associated mortality in our study were indeed much higher than those published in 11 European countries,[17] where 53.4% of preterm infants <32 weeks of gestation (n = 5697) had admission temperatures below 36.5°C, with only 12.9% below 35.5°C.[15] In California, hypothermia rates of 40% in early 2006 were reduced by half through a collaborative quality improvement project using a delivery room management package alone.[5,18] A similar approach could be adapted to our Ethiopian context.

Birth weight and gestational age are known risk factors for hypothermia and were therefore analyzed for an association with mortality within each stratum. A systematic review by Lunze et al reported that LBW, prematurity and intrauterine growth restriction were significantly associated with hypothermia and mortality.[19-22]

Table 3. Comparison of Mortality Rates in Hypothermic Versus Normal Temperature Babies by Gestational Age and by Birth Weight* Categories.

Gestational age (weeks)	Hypothermic			Normal			Association	
	N	Died	% Died	N	Died	% Died	OR	*P* value
<28	94	79	84.04	5	5	100.00	1.00	1.000
28-31	779	453	58.15	116	47	40.52	2.04	.000
32-34	1265	286	22.61	318	54	16.98	1.43	.030
35-36	853	121	14.19	271	30	11.07	1.33	.191
All	2991	939	31.39	710	136	19.15	1.93	.000
Birth weight (g)								
<1000	142	122	85.92	17	10	58.82	4.27	.000
1000-1499	806	418	51.86	141	56	39.72	1.64	.008
1500-2000	1367	301	22.02	330	44	13.33	1.84	.001
>2000	627	80	12.76	202	24	11.88	1.08	.743

*Sixty-nine preterm babies with missing birth weight information were excluded from the analysis.

Table 4. Follow-up of the Temperature After 12 Hours of Admission.

Temperature at admission		Temperature 12 hours after admission			
Status	N	Hypothermic	Normal	Fever	Missing
Hypothermic	2991 (80%)	1647 (55%)	714 (24%)	79 (3%)	551 (18%)
Normal	710 (19%)	214 (30%)	341 (48%)	24 (4%)	131 (18%)
Fever	57 (1%)	16 (28%)	19 (33%)	13 (23%)	9 (16%)
Total	3758	1877	1074	116	691

We confirmed the well-known inverse dose-response relationship with temperature in preterm neonates across gestational ages.[8,9] In addition, we showed a statistically significant associations of hypothermia with asphyxia (OR 2.6), RDS (OR 2.2), and resuscitation at birth (OR 1.3). In Nepal, in term and preterm neonates, resuscitation at birth also had an increased OR of 3.7 (95% CI: 1.5-8.8) for hypothermia.[9,10] Most, if not all available data suggest, however, that whenever the baby is separated from the mother, whether for asphyxia, resuscitation or RDS, particular attention needs to be given to its thermoregulation. A causality cannot be deferred as hypothermia may be secondary to asphyxia dysregulation[23] and RDS a compensation for increased oxygen requirements to fight hypothermia.[24]

In our study, out-born premature neonates only showed a trend for admission hypothermia compared to studies across gestational ages that showed statistical significance.[9,17] Interestingly, sepsis was negatively associated with hypothermia. Due to the design of the study, however, we cannot exclude the possibility that high temperature at admission prompted the sepsis diagnosis and may therefore not be considered an independent variable.

Several studies across all gestational ages, reported an association of hypothermia with mortality.[8,18,19,24,25] In a study in southern Nepal by Mullany et al, 92.3% of newborns had mild and 48.5% moderate to severe hypothermia, which was more often seen in the first 72 hours of life.[9,16] In this study, infants with a birth weight of 1000 to 1499 g with mild hypothermia (<36.5°C-36.0°C) had a mortality rate of 40.8% while in those with a temperature of <34.0°C, the mortality rate increased to 56.8%.

A study from Brazil showed that moderate hypothermia (32.0°C-35.9°C) at admission was an independent risk factor for neonatal death (AOR = 3.5, 95% CI: 3.2-3.8).[8] Even in the less severe ranges of hypothermia, in Iran, mortality was higher with admission temperatures below 36.5°C (8.8%) compared to normothermia (2.6%), but these results were not adjusted for birth weight and gestational age.[26] In Nigeria, a more than 2-fold greater mortality of 62.0% (OR = 2.3; 95% CI: 1.1-4.5) was reported in infants with hypothermia <36.5°C.[27] Similarly, in high-income countries, a population-based cohort study in USA showed a more than 10 times higher risk of mortality in VLBW infants compared to normal weight, whereas in babies born weighing between 1500 and 2000 g, mortality was 4 times higher.[28]

We showed a statistically significant association of mortality with any degree of hypothermia in preterm neonates, and as the admission body temperature decreased, the mortality increased in a dose-response relationship as shown across all gestational age neonates. Our study is one of the largest specifically reporting this dose-response of hypothermia on mortality in preterm neonates and makes a strong argument for avoiding over-simplified hypothermia categories in preterm infants similar to what was suggested by Sodemann et al.[16] Indeed, in our study as well as other reports,[8-10] very few babies had temperatures below 32°C, whereas neonatal mortality appears to increase very significantly within the WHO "moderate hypothermia" group.

In our study, 55% of hypothermic premature neonates remained hypothermic 12 hours later and roughly one-third of those who were normo- or hyperthermic became hypothermic. There are several factors that contribute to staying hypothermic even after admission: the oxygen they receive is not warmed and humidified in most of the NICUs; the room may not be thermoneutral for preterm babies; radiant warmers are not adequately available; continuous monitoring and adequate nursing care is not available, because the nurse to patient ratio is below the standard in most of the places especially during duty hours. Among the 701 infants with normal temperature and among the 57 infants who had hyperthermia at admission, 30% and 27%, respectively developed hypothermia. At admission most NICUs keep babies under a radiant warmer, since the monitoring system is poor and sensors sometimes may detach or not witnessed by health professionals they will be overheated and develop fever. We may also consider dehydration as a cause for the fever after 12 hours but overheating is the probable cause. In the HEAT trial at the Leiden University Medical Center, in Holland, infants with hypothermia at birth and at the time of admission also continued to be hypothermic longer than those without hypothermia.[28]

Conclusion

In conclusion, in a large study of preterm neonates in Ethiopia, we found a very high prevalence of hypothermia and confirmed the well-known dose-response relationship to mortality in the term population. Gestational age and birthweight were inversely correlated with hypothermia and death, as were resuscitation and RDS. Persistent hypothermia after 12 hours remained common and was observed more often in neonates with RDS.

Hypothermia remains a major issue in Ethiopia, particularly in preterm neonates, and is significantly associated with mortality. Quality of care projects in Ethiopian NICUs need to urgently address hypothermia prevention and treatment.

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Author Contributions

AGD: Contributed to conception and design; contributed to acquisition, analysis, and interpretation; drafted the manuscript; critically revised the manuscript; gave final approval; agrees to be accountable for all aspects of work ensuring integrity and accuracy. ZTB: contributed to the data interpretation, and statistical analysis of the data; critically revised the manuscript; gave final approval; agrees to be accountable for all aspects of work ensuring integrity and accuracy. YGF: contributed to the study design, data collection, data analysis, data interpretation, and writing of the manuscript; critically revised the manuscript; gave final approval; agrees to be accountable for all aspects of work ensuring integrity and accuracy. AKN: conceived the study, contributed to the study design, data collection, data analysis, data interpretation, and writing of the manuscript; critically revised the manuscript; gave final approval; agrees to be accountable for all aspects of work ensuring integrity and accuracy. EMM: conceived the study, contributed to the study design, data collection, data analysis, data interpretation, and writing of the manuscript; critically revised the manuscript; gave final approval; agrees to be accountable for all aspects of work ensuring integrity and accuracy. AM: conceived the study, contributed to the study design, data collection, data analysis, data interpretation, and writing of the manuscript; critically revised the manuscript; gave final approval; agrees to be accountable for all aspects of work ensuring integrity and accuracy. BW: conceived the study, contributed to the study design, data collection, data analysis, data interpretation, and writing of the manuscript; critically revised the manuscript; gave final approval; agrees to be accountable for all aspects of work ensuring integrity and accuracy. RP: conceived the study, contributed to the study design, data collection, data analysis, data interpretation, and writing of the manuscript; critically revised the manuscript; gave final approval; agrees to be accountable for all aspects of work ensuring integrity and accuracy. RLG: conceived the study, contributed to the study design, data collection, data analysis, data interpretation, and writing of the manuscript; critically revised the manuscript; gave final approval; agrees to be accountable for all aspects of work ensuring integrity and accuracy. LMM: conceived the study, contributed to the study design, data collection, data analysis, data interpretation, and writing of the manuscript; critically revised the manuscript; gave final approval; agrees to be accountable for all aspects of work ensuring integrity and accuracy.

Declaration of Conflicting Interests

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Ethics Approval and Consent to Participate

This study was approved by the ethical review committees of participating institutions (Addis Ababa University, Jimma University and the University of Gondar, Ethiopia). Informed consent was obtained from all participants.

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