ORIGINAL ARTICLE

Distribution and outcomes of neonatal admission hypothermia in a tertiary hospital in Jos Nigeria

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Abstract

Background: Admission hypothermia (AH) is common and associated with adverse neonatal outcomes. The association of severity of AH with mortality is emerging however, the widely used WHO classification of neonatal hypothermia has limitations. We therefore sought to determine the severity distribution of AH, agreement between the two methods of classification and estimate risk of mortality in hospitalised neonates.

Methods: It was a retrospective crossectional study of 540 neonatal admissions. Anonymized data extracted from the unit electronic records. The WHO method was compared with a new method of classification of hypothermia.

Results: The prevalence of AH was 41.9% with 104 (48.0%), 88(38.9%), 23(10.2%) and 11(4.9%) neonate with Grade I(mild), Grade II, Grade III, and Grade IV (severe) AH respectively. There was moderate agreement between both methods of classifications ($\kappa = 0.740$, $p < 0.001$). Mortality was 3.4 folds in neonates with AH (16.8%) compared to those with normothermia (5.6%) (crude odds ratio [cOR] =3.381, 95% CI= 1.677-6.816). The proportion of mortality increased with severity of hypothermia with mortality rates of 14.4%, 15.9%, 21.7% and 36.4% in neonates with Grade I, Grade II, Grade III and Grade IV hypothermia respectively (χ^2 for trends= 16.407, p=<0.001). After correcting for the effect of admission age, gestational age and birth weight, there was a 6 fold increase in the risk of mortality in neonates with Grade IV(severe) AH (adjusted OR = 6.393, 95%CI= 1.552- 26.331).

Conclusion: The new method had an advantage of identifying a subpopulation of neonates with severe AH with increased risk of mortality therefore recommended.

Keywords: Hypothermia, neonates, neonatal mortality, mortality risk

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Introduction

Neonatal mortality accounts for forty six percent of the 5.3 million child deaths globally.[1] There exists wide regional and national differences in neonatal deaths with 57% of the 2.5 million neonatal deaths occurring in Sub-Saharan Africa.[2] In particular, Nigeria has the second highest number of neonatal deaths globally.[3] Increased access to good quality care and targeted interventions have the potential to avert about two thirds of these deaths principally resulting from-prematurity, intrapartum complications and infection.[4] In addition, identifying those at risk of mortality could help provide focussed care especially in resource poor settings.

Admission hypothermia (AH) is defined by the World Health Organization (WHO) as axillary temperature <36.5°C.[5] Recent studies showed that the point prevalence of AH amongst total neonatal admissions ranges between 22 and 82%.[6-10] In addition, AH has clearly been shown to predict neonatal deaths.[6,11,12] Other adverse outcomes associated with AH include respiratory distress syndrome, asphyxia, broncho-pulmonary dysplasia, sepsis and retinopathy of prematurity especially in very low birth weight (VLBW) infants.[13-16]

There appears to be growing evidence that the risk of adverse outcomes is proportional to severity of AH.[11,16] Chang *et al* [16] reported that mild AH was not associated with short or long term outcomes in VLBW neonates while moderate AH was associated with asphyxia, RDS and mortality. However, studies comparing neonatal mortality with increasing severity of AH are few. Also, the WHO classification of hypothermia has been criticized for including within the moderate hypothermia class (32-35.9°C) exposures that have significantly different risks of neonatal mortality.[17,18] Furthermore, the unavailability of low reading thermometers in most resource-poor settings as well as unrealistically low proportions of neonates with severe hypothermia make the cut of 32°C for severe hypothermia impractical.[8,10,19] Mullany *et al*,[17,20] developed a modified classification for hypothermia which accommodates these drawbacks of the WHO classification by including a subclass in the moderate class of original WHO classification and increasing the cut off for severe hypothermia from 32°C to 34°C.[20]

We therefore undertook this study to determine the severity distribution of AH, agreement between the two methods of classification and estimate risk of mortality using the modified classification. We hope the findings of our study will provide additional clinical guidance in our setting for risk stratified treatment of neonates with

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AH and program managers in designing intervention activities in order to reduce AH-attributable neonatal morbidity and mortality in resource limited settings.

Methods

Study Design and Period: The study used a single hospital-based retrospective cross-sectional analytical design and was carried out over a 19 month period (1st July 2020 - 31st January 2022).

Study Setting: The study was carried out in the neonatal unit of Jos University Teaching Hospital (JUTH) which is located in Jos, North-central Nigeria. The hospital is a 600 bedded government-owned tertiary health facility with a 30 bedded Special Care Baby Unit (SCBU). Jos is unique with a cold climate than most parts of Nigeria largely from her high altitude with mean minimum and maximum temperatures of 16 and 26°C respectively.[21] As part of standard of care, axillary temperature is measured using a clinical digital thermometer (ME4201 measurement range 32-42°C) usually kept in place until it beeps (takes 1-2 minutes). Temperature readings are usually recorded at admission, 6 hourly for monitoring and during reviews.

Minimum Sample size calculation: The minimum sample size of 359 was calculated using the Kish and Leslie formula for single proportions with power set at 80% and confidence level of 95% with the highest reference prevalence of AH of 62% for whole neonatal population.[8]

Study Population: The study involved neonates (aged 0-28 days) admitted into the unit.

Inclusion Criteria: All consecutive neonates admitted into the unit during the study period.

Exclusion Criteria:

1. Incomplete information about temperature recording at admission or admission outcome
2. Patients who were discharged against medical advice

Data Collection: Data was collected from unit electronic database. Variables extracted include: temperature at admission (AH), mother's age, and sociodemographic variables, infant's age at admission, sex, place of birth (inborn/outborn), weight on admission, and gestational age at birth (by Last menstrual period or Ballard score).

Operational Definition of Variables

Admission hypothermia was defined as axillary temperature <36.5°C at admission.[5] The WHO classification of hypothermia used was as follows: mild (36.0-36.4°C), moderate (32-35.9°C) and severe (<32°C) as defined by WHO.[5] The second classification used as modified by Mullany *et al* was Grade I (36.0-36.4°C), Grade II (35.0-35.9°C), Grade III (34.0-34.9°C) and Grade IV (<34°C).[17,20] Normothermia was defined as 36.5-37.5°C and hyperthermia was >37.5°C.[5]

Ethical Considerations and Permissions

Ethical clearance was obtained from the Ethical Review Board of Jos university Hospital and permission to use unit data was obtained from the unit head. All data were de-identified before data analysis.

Data Analysis

Data was entered into Microsoft Excel 2013 and analysed using SPSS version 25 (IBM corporation, 2017) Descriptive variables were presented in terms of proportions. Primary outcome variable was mortality at discharge and presented in percentage of admission. Independent variables were categorical. Cohen kappa statistics (κ) was used to assess degree of agreement between the two methods of classification of hypothermia. McHugh's interpretation of κ was used in this study.[22] Bivariate and multivariate logistic regression was used to test for association between AH and mortality. Neonates admitted with hyperthermia were excluded in the logistic regression models (ie outcome in neonates with hypothermia was compared to those with normothermia). Only variables with a p value of <0.05 from the bivariate analysis were included in the multivariate model. Due to the close association between prematurity and admission weight, they were included in separate logistic regression models to avoid undermining their effect due to multicollinearity. A p-value of 0.05% was considered statistically significant.

Results

Out of a total of 606 neonatal admissions, 540 were included after excluding 44 for missing information about AH and 22 who were discharged against medical advice. (Figure 1). About 90% of the mothers were aged between 20 and 39 years and a third had primary education (35.2%). Almost half (46.9%) of the neonates were admitted within 24 hours of life. Also, 36.9% and 48.0% of the neonates were preterm or had an admission weight <2.5kg respectively. (Table 1).

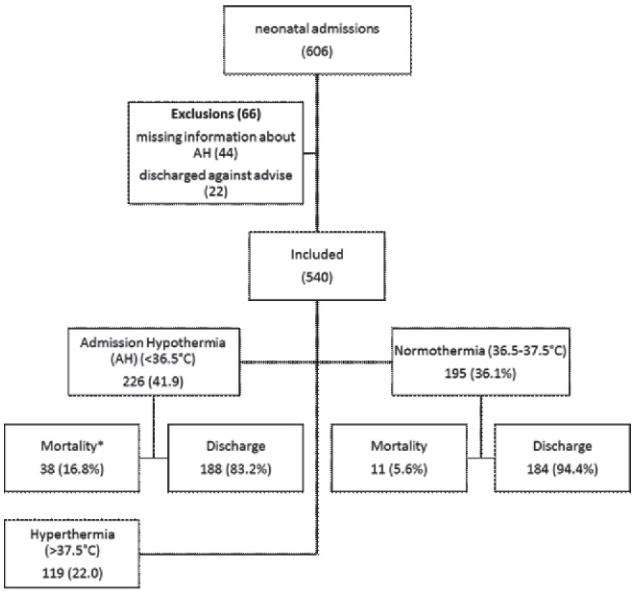
A total of 226 (41.9%) had AH with 38(16.8%) deaths which was 3.3 times higher than 11(5.6%) deaths in neonates with normothermia (crude odds ratio [cOR] =3.381,95% CI=1.677-6.816). (Figure1). Table 2 compares the distribution of neonates with hypothermia using the two methods of classification of hypothermia. The main difference is in the distribution of those with moderate hypothermia according to the WHO classification. There was moderate agreement between

both methods of classifications (κ = 0.740, p <0.001). There was a significantly increasing trend in mortality with increasing severity of hypothermia with mortality rates of 14.4%, 15.9%, 21.7% and 36.4% in neonates with Grade I, Grade II, Grade III and Grade IV hypothermia respectively (χ^2 test for-trend= 16.407, p=<0.001). (Table 3)

Table1. Socio-demographic Characteristics of Studied neonates (n=540)

Variable	Frequency (%)
Maternal age (years)	
<20	11 (2.1)
20-29	224 (43.2)
30-39	246 (47.4)
≥40	38 (7.3)
Educational level	
No formal education	124 (29.7)
Primary	147 (35.2)
Secondary	59 (14.1)
Tertiary	88 (21.1)
Parity	
1	183 (35.4)
2-4	264 (51.1)
>4	70 (13.5)
Age (days)	
<1	253 (46.9)
1-7	209 (38.7)
8-28	78 (14.4)
Sex	
Male	296 (55.4)
Female	238 (44.6)
Gestational Age (weeks)	
<28	11 (2.0)
28-32	53 (9.9)
33-36	133 (24.7)
≥37	341 (63.1)
Admission weight (g)	
<2500	252 (48.0)
≥2500	273 (52.0)
Place of Birth	
Inborn	224 (46.9)
Outborn	254 (53.1)

Following univariate logistic regression, the odds of mortality was significantly higher in neonates with Grade I (cOR= 2.819, 95%CI= 1.244-6.389), Grade II (cOR= 3.165, 955CI= 1.374-7.290), Grade III (cOR= 4.646, 95%CI= 1.453-14.562) and Grade IV (cOR= 9.558, 95%CI= 2.427-37.648) AH respectively.(Table3) Having adjusted for the effect of age at admission, gestational age and admission weight which were significantly associated with mortality in univariate analysis, only grade IV AH was significantly associated with mortality compared to those who had normothermia (adjusted OR = 6.393, 95%CI= 1.552-26.331). (Table 4)



*OR= 3.381, 95%CI= 1.677-6.816, $\times^2$= 12.707, p value=0.001

Figure1. Flowchart of studied neonates.

Discussion

Our study reiterates the high prevalence of admission hypothermia among neonates managed in the unit and its association with mortality. The current study is one of the few in this region that describe an association between severity of AH and mortality.

The prevalence of hypothermia in our study was 41.9% which echoes the huge burden even in the Tropics with higher ambient temperature and consistent with other studies in Nigeria (62%), Ethiopia (64%), and Uganda (51%) irrespective of birth weight.[7,8,23] A combination of behavioural, environmental and physiological factors are responsible for the high burden. These factors include prematurity, low birth weight, home births, delayed initiation of breastfeeding, inadequate clothing and presence of comorbidities in the neonate or mother.[6,23-25]

A major challenge limiting comparability of findings from studies on neonatal hypothermia has been the use of different thresholds ranging from 35 to 36.5°C.[26-29] Therefore, many authors readily accepted the

Table 2. Relationship between WHO and Revised Classification of Hypothermia (°C)

	Grade I (36.0- 36.4)	Grade II (35.0-35.9)	Grade III (34.0-34.9)	Grade IV (<34.0)	Total
Mild (36.0-36.4)	104 (100%)	0	0	0	104 (46.0%)
Moderate (32-35.9)	0	88 (72.1%)	23 (18.9%)	11 (9.0%)	112 (54.0%)
Total	104 (48.0%)	88 (38.9%)	23 (10.2%)	11 (4.9%)	226 (100%)

K= 0.740, p value <0.001

Table 3. Bivariate analysis of association between admission hypothermia and mortality in studied neonates

Variable	Deaths(%)	Discharges(%)	cOR (95%CI)	p value
Hypothermia(°C)				
36.5 - 37.5	11(5.6)	184(94.4)	1.000	
36.0 - 36.4	15(14.4)	89(85.6)	2.819 (1.244-6.389)	0.013
35.0 - 35.9	14(15.9)	74(84.1)	3.165 (1.374-7.290)	0.007
34.0 - 34.9	5(21.7)	18(78.3)	4.646 (1.453-14.862)	0.010
<34.0	4(36.4)	7(63.6)	9.558 (2.427-37.648)	0.001
Maternal Age (yrs)				
<20	1(9.1)	10(90.9)	0.660 (0.069-6.329)	0.719
20-29	25(11.2)	199(88.8)	0.829 (0.296-2.319)	0.721
30-39	28(11.4)	218(88.6)	0.848 (0.306-2.350)	0.751
≥40	5(13.2)	33(86.8)	1.00	
Education				
NFE	18(14.5)	106(85.5)	1.189 (0.531-2.660)	0.674
Primary	12(8.2)	135(91.8)	0.622 (0.262-1.477)	0.282
Secondary	8(13.6)	51(86.4)	1.098 (0.413-2.917)	0.851
Tertiary	11(12.5)	77(87.5)	1.000	
Parity				
1	19(10.4)	164(89.6)	0.785 (0.337-1.829)	0.575
1-4	28(10.6)	236(89.4)	0.804 (0.361-1.793)	0.594
>4	9(12.9)	61(87.1)	1.000	
Age (days)				
< 1	40(15.8)	213(84.2)	2.742 (1.043-7.211)	0.041
1-7	14(6.7)	195(93.3)	1.048 (0.365-3.013)	0.930
8-28	5(6.4)	73(93.6)	1.000	
Sex				
Male	33(11.1)	263(88.9)	1.0123 (0.593-1.764)	0.935
Female	26(10.6)	212(89.1)	1.000	
Gestational age (wks)				
<28	6(54.5)	5(45.5)	15.168 (4.325-53.193)	<0.001
28-32	12(22.6)	41(77.4)	3.700 (1.728-7.921)	0.001
33-36	16(12.0)	117(88.0)	1.729 (0.891-3.352)	0.105
≥37	25(7.3)	316(92.7)	1.000	
Admission weight				
<2.5	38(15.1)	214(84.9)	2.246 (1.269-3.977)	0.005
≥2.5	20(7.3)	230(90.6)	1.000	
Place of birth				
Inborn	21(9.4)	203(90.6)	1.009 (0.545-1.866)	0.978
Outborn	24(9.4)	230(90.6)	1.000	

#$\chi 2$ for trend= 16.407, p=<0.001, cOR= crude odds ratio, aOR= adjusted odds ratio (aOR1 model 1 excludes admission weight; aOR2 model 2 excludes gestational age)

Table 4 Multiple Logistic Regression of association between Admission hypothermia and risk of mortality

Variables	aOR1 (95%CI)	p value	aOR2 (95% CI)	p value
Hypothermia(°C)				
36.5 - 37.5	1.000		1.000	
36.0 - 36.4	2.358 (0.991-5.608)	0.052	2.326 (0.990-5.462)	0.053
35.0 - 35.9	2.012 (0.784-5.160)	0.146	2.075 (0.830-5.188)	0.118
34.0 - 34.9	3.191 (0.884-11.518)	0.076	2.788 (0.811-9.588)	0.104
<34.0	5.991 (1.357-26.456)	0.018*	6.393 (1.552-26.331)	0.010*
Age (days)				
< 1	2.613 (0.556-12.296)	0.224	3.043 (0.677-13.666)	0.147
1-7	1.714 (0.347-8.469)	0.509	1.778 (0.359-8.808)	0.481
8-28	1.000		1.000	
Gestational age (wks)				
<28	10.120 (2.336-43.841)	0.002*		
28-32	1.968 (0.781-4.960)	0.151		
33-36	0.878 (0.379-2.033)	0.762		
≥37	1.000			
Admission weight				
<2.5			0.736 (0.365-1.485)	0.392
≥2.5			1.000	

WHO definition and classification which resolved the issue of comparability. Our study made use of a modified WHO classification which further subdivided moderate hypothermia in the WHO classification into 2 sub-classes and raised the threshold of severe hypothermia.[17] There was substantial agreement between the two classification methods in our study. The modified classification identified more infants with severe hypothermia which is an advantage over using a lower threshold. To the best of our knowledge, this is the first study that tried to assess the degree of agreement between the two methods of classification of severity.

In our study, there was a 3 fold odds of mortality in neonates with AH. This is similar to a study by Manji et al which reported a 3 fold risk of mortality in neonates with AH in a Tanzania tertiary hospital. In that study, AH was also associated with longer hospital stay and higher postnatal weight loss.[6] In Kenya, there was a 20 fold chance of survival in neonates without AH within the first 24 hours after birth.[30] The high risk of mortality reported in that study may be because studied neonates were followed up for the first 24 hours after birth when neonates are at highest risk of AH and mortality.[16,17,24,26] Just as seen in our study, the highest risk of mortality was seen in very preterms. In addition, nonadherence to WHO warm chain increased risk of AH. A systematic review and meta-analysis reported an aOR of 1.89 of mortality in very low birth weight neonates with AH.[31] Another study reported a 3 fold increase in risk of death in outborn neonates with AH.[26] It is also noteworthy that some studies did not find significant associations of AH with mortality.[15,23] One of such studies was amongst Danish preterm very low birth weight neonates. However, the effect of AH could have been dampened by including both gestational age and birth weight in the multiple logistic model.[15] This was managed in our study which included them one at a time.

One of the rationale for the current study was to bridge the knowledge gap about the association between severity of AH and mortality. The odds increased progressively from 2.8 in those with Grade I (mild) AH to almost 10 fold in those with Grade IV (severe) AH but after multiple logistic regression, only severe AH was associated with mortality. The risk of mortality was 1.8 fold in mild AH and 4 fold in VLBW neonates with moderate AH in a study in China.[32] Another study, in VLBW infants reported 38%, 44% and 86% increase in the odds of mortality in those with temperatures of 36.0-36.4°C, 35.0-35.9°C, and <35°C at admission.[13] Also, Mullany, et al, in a secondary analysis of data from a community based study using the modified classification, demonstrated exponentially increasing risk of mortality for every degree decrease in temperature with a 9 fold increased risk of mortality in neonates with Grade IV hypothermia.[17]

As a result of the increased risk of mortality with

increasing deviation of hypothermia, recommendations using a graded approach to institute management and preventive interventions have been developed. One community-based guideline recommends in-home thermal care interventions for term infants with up to Grade 3 and preterm with grade 2 hypothermia and immediate skilled care and referral for those with lower temperatures.[17] For hospitalized neonates, the use of plastic bags has been shown to effectively prevent hypothermia especially in very low birth weight infants.[33] There is however, emerging evidence about the use of external heat sources such as skin-skin care, thermal mattresses and a combination of methods in preventing hypothermia as well as resultant mortality.[33]

Ours being a retrospective study was limited in the standardization of measurement of temperature. Although the axillary route is the method used to measure temperature in our unit, the timing within the admission period (which could take upto 2 hours for some infants) was not specified. Also data on confounders such as duration of hypothermia and interventions to prevent and manage hypothermia were unavailable.

Conclusion

Hypothermia at admission is common in hospitalized neonates in our setting. Mortality is increased in neonates with AH. The new method of classification of severity of hypothermia has moderate degree of agreement with the WHO classification and has the advantage of identifying neonates with severe hypothermia which was associated with increased risk of mortality in the studied neonates. We therefore support the recommendation of the use of this classification in low resource settings.

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