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Original Article

Paediatrics Section

Effect of Admission Hypothermia on Short-term and Long-term Outcomes in Neonates Admitted at a Tertiary Care Hospital

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ABSTRACT

Introduction: Neonatal hypothermia is an abnormal thermal state in which body temperature drops below 36.5°C leading to adverse clinical outcomes caused due to prematurity of the neonate or severe infection. Since, the outcome of hypothermia is not immediately detected, it relatively gets neglected by the health care provider.

Aim: To investigate the effect of admission hypothermia on short-term and long-term outcomes in neonates admitted at a tertiary care hospital.

Materials and Methods: The descriptive study was conducted on 189 neonates with admission hypothermia which were further grouped into various grades of hypothermia and were followed-up to determine the outcome. The study population was subjected to routine investigations as per protocol. All neonates were screened by Ultrasonography (USG) cranium, 2D Echocardiogram (2D ECHO) and Retinopathy of Prematurity (ROP) screening. At each follow-up they underwent various neurological examination at 3, 6, 9 and 12 months of age, neurodevelopment assessment using DAS II at one year of age, growth assessment (detailed anthropometry) and developmental milestones, nutritional assessment (breastfeeding or weaning), retinopathy of prematurity screening at three weeks. At 12 months of age, all the babies were assessed using Developmental Assessment scale for Indian infants. The data was analysed by using Statistical Package for the Social Sciences (SPSS) Version 21.0 for data computation, p=value <0.05 was considered as statistically significant.

Results: Two third (63.5%) of the neonates admitted in the NICU with admission hypothermia were males. Overall, 63% of admitted neonates with hypothermia were low-birth weight. Among the short-term outcome in neonates the most common was the Respiratory Distress Syndrome (RDS,81%). Most common combination of the short-term outcome were RDS+Patent Ductus Arteriosus (PDA)+Sepsis (n=6) and RDS+PDA+ROP Grade II (n=4), and RDS+Intraventricular Haemorrhage (IVH)+Sepsis (n=2). All the neonates 4(100%) who were extremely preterm developed RDS compared to other neonates. RDS was cause of death in 4 hypothermic neonates. The mean development age using DAS II was 11.8 months. The mean development quotient was 94.

Conclusion: The present observational study demonstrates a relationship between admission hypothermia and the type of neonatal morbidity and mortality. Gestational age carried a significant relationship with the short-term outcome like RDS in terms of developing co-morbidities and their survivability but had a limited role in development of long-term outcome. Routine screening of temperature and early intervention prevents the development of hypothermia thus preventing short-term complications. There is a need to create awareness among health professionals about the dangers of hypothermia so that early intervention could be undertaken to reduce its complications.

Keywords: Growth, Nutrition, Respiratory distress syndrome

INTRODUCTION

The importance for thermal newborn protection has long been known, as described by Soranus of Ephesus (98 to 138 AD) in his four volume 'On Diseases on Women', which talks about the importance of keeping newborns warm [1]. A major challenge faced by developing nations in newborn survival is a lack of a proper thermal protection [1]. In modern times, the majority of almost 4 million newborns globally who do not survive their first month of life die of complications associated with hypothermia, such as prematurity and severe infections (mostly sepsis and pneumonia) [2,3]. A review published in 2013 have acknowledged that neonatal deaths related to hypothermia is relatively neglected, but considered it easily preventable if attention to warmth, feeding and infection management are given [4]. Neonatal hypothermia may also set in due to inadequate care and lack of attention by the hospital personnel during childbirth [5].

The first few minutes after the birth of a neonate are the most crucial time for newborn survival as this is the time where the transition period for a completely new adaptation from intra-uterine to extra-uterine takes place. A combination of physiological, behavioural and environmental factors is basically responsible for putting a newborn at risk of developing hypothermia, irrespective of their weight at the time of birth [6]. The thermoregulatory mechanisms in premature and low-birth weight infants get exhausted easily leading to death due to hypothermia or death due to sepsis [7]. Admission hypothermia in newborns rarely leads to death directly but presence of various co-morbid conditions along with birth asphyxia, neonatal infections, and preterm birth, attributes to a substantial amount of mortality [1].

A few researches are available on short-term outcomes of hypothermia. It has been found that hypothermia is significantly related to mortality [8] and morbidities like Necrotising Enterocolitis (NEC) [8-10], late-onset sepsis [10] and Intraventricular Haemorrhage (IVH) [11], in neonates. But there is limited information on long-term impact of admission hypothermia on young children. Available studies on admission hypothermia primarily focused on the impact of admission hypothermia in low-birth weight newborns or very low-birth weight newborns [12,13].

In this study, an attempt was made to investigate the outcomes of admission hypothermia in neonates admitted in the study hospital and to determine the association of admission hypothermia with the short-term and long-term outcomes of the neonate.

MATERIALS AND METHODS

The descriptive analysis of a prospective observational study was conducted in the Neonatal Intensive Care Unit (NICU) of Department of Paediatrics at Geetanjali Medical College and Hospital (GMCH), Udaipur, Rajasthan, India from January 2019 to June 2019. Study population consisted of neonates delivered at GMCH and admitted to NICU with admission temperature less than 36.5°C. A clearance from ethical committee (GU/HREC/EC/2019/1633) of institute was obtained. Written informed consent was taken from all the patients or their family for participation in the study.

Inclusion criteria: All neonates delivered and admitted to NICU of GMCH with (axillary) body temperature <36.5°C.

Exclusion criteria: Outborn neonates and neonates with gross congenital malformation.

Sample size calculation: The prevalence of hypothermia in neonates was found to be 60% [14]. Considering 95% of confidence level, 80% power, and 10% margin of error a sample of 189 or more neonates with hypothermia was calculated as per using the given statistical formula:

$$n=\frac{(Z_{\alpha}+Z_{1-p})2\ p\ (1-p)}{E^2}$$

Parameters studied were identification information In pateint Department (IPD) number, date of admission, mothers name and age were recorded. Obstetric history, gestational age, gravida, parity information were recorded. Other history of medical illness like diabetes, hypertension, thyroid disorders, asthma etc. major abdominal surgeries and blood group collected. Birth notes, date and time of birth, gender, birth weight, mode of delivery (spontaneous vaginal/induced vaginal/forceps vaginal/C-section) were also recorded.

Study Procedure

Admission temperature of each neonate were taken manually by thermometer at the time of admission to NICU. Axillary temperature was taken using digital thermometers and measured in degrees Celsius. Admission temperature was the first measure taken at the time of admission to the NICU.

The study population was divided into extremely preterm (<28 weeks), very preterm (28 to <32 weeks), moderate or late preterm (32 to <37 weeks) and term (37 to 42 weeks) [15]. The study population was divided according to the WHO classifications of hypothermia which are: (1) mild hypothermia or cold stress: 36.0 to 36.4 °C (96.8 to 97.5°F); (2) moderate hypothermia: 32.0 to 35.9°C (89.6 to 96.6°F); and (3) severe hypothermia: below 32 °C (<89.6°F) [16].

The study population was subjected to routine investigations as per protocol. 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 and neonatal conditions were recorded. Detailed history and clinical examination were performed. All neonatal complications were recorded during the course of their admission in NICU. Patient underwent routine investigation which consisted of complete blood count, urine routine and microscopy with culture. All neonates were screened by USG cranium, 2D ECHO and ROP screening. Ultrasonography was done under guidance of qualified radiologist in Department of Radiodiagnosis.

Neonates who had specific morbidities were treated accordingly. After discharge they were followed-up to 1 year. During follow-up growth and developmental assessment was done. A detailed history and neurological examination was done to detect neurological deficit and tone abnormalities. All cases were screened in high-risk follow-up clinic by neonatologist at 3, 6, 9 and 12 months of age (corrected age of 40 weeks for preterm and chronological age for term infants). They underwent the following examination at each follow-up:

Retinopathy of prematurity screening was conducted at three weeks and subsequently as per protocol [17]. Neurodevelopment

assessment at one year of age was done for all the babies, using Developmental Assessment scale for Indian infants [18]. Abnormal neurodevelopment was diagnosed if any one of the following abnormalities are identified (1) MoQ or MeQ of less than 70% on DAS II [19] (2) Visual impairment.

Development assessment was done using Trivandrum development screening chart. It consists of 17 items. The range for each test item was taken from the norm given in the Bayley scale of infant development (Baroda norms) [20].

STATISTICAL ANALYSIS

Data analysis was done by Statistical Package for the Social Sciences (SPSS) version 21 statistical software. Categorical data were expressed as frequency and percentage and their comparison were done by Chi-square test. The distribution of data for continuous variables were expressed by mean and standard deviation and their comparison was done using Student t-test. All analysis was carried out at 5% of significance and $p<0.05$ was considered to be significant.

RESULTS

[Table/Fig-1] shows that thyroid disorder constituted the largest percentage 55 (29.1%) of maternal conditions, primiparous mother constituted 124 (65.60%) of total pregnancies, Lower segment caesarean section (LSCS) constituted 133 (70.37%) of total deliveries, maximum number of deliveries happened in day time 105 (55.55%).

[Table/Fig-2] shows male constituted 63.49% (120) of the total population. 4 (2%) who were admitted were extremely preterm <28 weeks; 8 (4%) of neonates weighed less than one kg. [Table/Fig-3] shows that 60% of neonates in the study were in mild hypothermia (36.0-36.5°C). [Table/Fig-4] shows that highest percentage of neonates with hypothermia had RDS (8%) followed by sepsis (22.2%).

[Table/Fig-5] shows RDS was seen in four neonates where one neonate had PDA and developed sepsis and RDS and one neonate PDA and developed IVH and RDS. Two hypothermic neonates died of RDS, one on day 7th and other on day 8th after birth.

[Table/Fig-6] shows that RDS was present in all the neonates (100%) who were <28 weeks followed by neonates who were within 28 to 32 weeks gestation (87.75%) and was least in neonates of 37 to 42 week gestation (73%). A 75% (3 out of 4) neonates were in moderate hypothermia whose gestational age was <28 weeks. Most of the neonates with RDS whose gestational age was more than 28 weeks had mild hypothermia.

[Table/Fig-7] In the present study, 42 (22%) of neonates suffered from sepsis. In the present study sepsis was second most common short-term outcome among the neonates admitted with admission hypothermia. Sepsis was maximum in neonates

Variables	Number	Percentage (%)
Maternal conditions		
Thyroid disorder	55	29.1
Gestational hypertension	47	24.9
OS Tightening	20	10.6
Diagnostic hystero-laparoscopy	13	6.9
Gestational diabetes mellitus	8	4.2
Inflammatory Bowel Disease (IBD)	4	2.1
Diabetes mellitus	2	1.1
Asthma	2	1.1
Chicken pox	2	1.1
Dilated cardiomyopathy	2	1.1
Epilepsy	1	0.5
Polycystic ovarian disease	1	0.5
Parity		
Primiparous	124	65.60
Multiparous	65	34.39
Mode of delivery		
Lower segment caesarean section	133	70.37
Normal vaginal delivery	56	29.62
Time of delivery		
Day	105	55.55
Night	84	44.44

[Table/Fig-1]: Obstetrics characteristics of mother of the neonates.

Variables	Number	Percentage (%)
Gender		
Male	120	63.49
Female	69	36.51
Gestational age (week)		
<28	4	2
28 to 32	49	26
32 to 37	58	31
37 to 42 (term)	78	41
Birth weight (Kg)		
<1	8	4
1.0 to 1.5	25	13
1.5 to 2.0	49	26
2.0 to 2.5	38	20
2.5 to 3.0	43	23
3.0 to 3.5	17	9
3.5 to 4.0	6	3
>4	3	2

[Table/Fig-2]: Demographic distribution of the neonates (N=189).

Grading of hypothermia	Number of neonates	Percentage (%)
Mild (36.0-36.4°C)	114	60
Moderate (32.0-35.9°C)	75	40
Total	189	100

[Table/Fig-3]: Hypothermia profile of children.

Short-term outcomes	Number	Percentage (%)
Respiratory Distress Syndrome (RDS)	153	81.0
Sepsis	42	22.2
Necrotising Enterocolitis (NEC)	15	7.9
Retinopathy of Prematurity (ROP) Grade II	7	3.7
Death	6	3.2
Severe intraventricular haemorrhage	5	2.6
Transient Tachypnoea of Newborn (TTN)	2	1.1
Bleeding diathesis	2	1 %

[Table/Fig-4]: Short-term outcomes of hypothermia.

Cause of death	Total death of neonates	Age at death	
RDS+sepsis+PDA	1	5th day	
RDS+IVH+PDA	1	2nd day	
RDS	2	7th day	8th day
Sepsis	2	7th day	10th day

[Table/Fig-5]: Cause of neonatal death and age of death.
RDS: Respiratory distress syndrome; PDA: Patent ductus arteriosus; IVH: Intra ventricular haemorrhage

Gestational age (week)	RDS in all hypothermics (Number=153) (%)	Mild hypothermia N=95	Moderate hypothermia N=58
<28	4 (100%)	1 (1.05%)	3 (5.17%)
28 to <32	43 (87.75%)	24 (25.26%)	19 (32.75%)
32 to <27	49 (84.48%)	37 (38.94%)	12 (20.68%)
37 to 42	57 (73.07%)	33 (34.73%)	24 (41.37%)

[Table/Fig-6]: Gestational age-wise distribution of Respiratory Distress Syndrome (RDS) (N=153).

Gestational age (week)	Sepsis in all hypothermics (N=42)	Mild hypothermia N=26	Moderate hypothermia N=16
<28	1 (25%)	1 (3.8%)	0
28 to <32	19 (38.77%)	11 (42.30%)	8 (50%)
32 to <37	20 (34.48%)	13 (50%)	7 (43.75)
37 to 42	2 (2.56%)	1 (3.8%)	1 (6.25%)

[Table/Fig-7]: Gestational age-wise distribution of sepsis.

of 28 to <32 week age group 19 (38.77%) and least 2 (2.56%) in neonates with 37 to 42 week gestational age. Out of 26 neonates in mild hypothermia 1 (3.8%) was below 28 week gestation and 13 (50%) neonates were in 32 to <37 week gestation. No neonates <28 week gestation had moderate hypothermia.

[Table/Fig-8] C-reactive Protein (CRP) level was found raised in all cases of sepsis. Nine (21%) cases of sepsis were reported with culture negative findings. *Escherichia coli* in 23 (55%) neonates was the most common infection found in the culture testing.

Variable			Sepsis present (number=42)
CRP	Within normal range (<10 mg/L)		0
	Above the normal range (≥10 mg/L)		42 (100%)
Culture	Culture negative		9 (21%)
	Culture positive	*Klebsiella*	8 (19%)
		Escherichia coli	23 (55%)
		Pseudomonas	2 (5%)

[Table/Fig-8]: Presence of sepsis with CRP and culture results.

[Table/Fig-9] shows that a total of 5 (2.6%) neonates were detected with IVH using cranial USG. All 5 neonates with IVH were in the moderate category of hypothermia (100%). Out of five, 2 (40%) were below the 28 weeks of gestation and rest 3 (60%) were between 28 to 32 weeks of gestation.

IVH	IVH in all hypothermics number (%)	Mild hypothermia	Moderate hypothermia
<28 week	2 (40%)	0	2 (40%)
28 to <32 week	3 (60%)	0	3 (60%)
32 to <37 week	0	0	0
37 to 42 week	0	0	0

[Table/Fig-9]: Distribution of Intra Ventricular Hemorrhage (IVH).

[Table/Fig-10] shows eleven hypothermic neonates with ROP Grade II. A total of 4 (100%) neonates with gestational age <28 weeks had ROP. No neonates were detected with ROP above 32-week gestation. Maximum percentage of neonates with ROP had moderate form of hypothermia.

ROP grade II	All hypothermics N (%)	Mild hypothermia N=4	Moderate hypothermia N=7
<28 week	4 (100%)	1 (25%)	3 (42.85%)
28 to <32 week	7 (14.28%)	3 (75%)	4 (57.14%)
32 to <37 week	0	0	0
37 to 42 week	0	0	0

[Table/Fig-10]: Distribution of ROP Grade II.
ROP: Retinopathy of prematurity

[Table/Fig-11] Top three most common combination of the short-term outcome were RDS+PDA+Sepsis {6 (3.17%) out of 189} and RDS+PDA+ROP Grade II {4 (2.11%)}, and RDS+IVH+Sepsis {2 (1.05%)}. 16 neonates reported combination of three short-term outcome in the study and three neonates reported combination of four short-term outcomes.

[Table/Fig-12] The mean development age was 11.8 months. The mean development quotient was 94.

Independent morbidities and combinations of the short-term outcomes of hypothermia	N (%)
RDS+PDA+Sepsis	6 (3.17%)
RDS+PDA+ROP Grade II	4 (2.11%)
RDS+IVH+Sepsis	2 (1.05%)
RDS+ASD+PDA	1 (0.52%)
NEC+RDS+Sepsis	1 (0.52%)
IVH+RDS+PDA	1 (0.52%)
RDS+NEC+PDA	1 (0.52%)
RDS+ASD+VSD+PDA	1 (0.52%)
RDS+ROP Grade II+Sepsis+PDA	1 (0.52%)
IVH+ ROP Grade II+RDS+PDA	1 (0.52%)

[Table/Fig-11]: Independent and combinations of three or more short-term outcomes.
PDA: Patent ductus arteriosus; NEC: Necrotising enterocolitis; VSD: Ventricular septal defect

Variables	
Developmental assessment by using DAS II	n=170
Mean developmental age	11.8±0.56 months
Developmental quotient	94

[Table/Fig-12]: Developmental assessment of neonates admitted in NICU with admission hypothermia at the age of one year (N=170).

DISCUSSION

Admission hypothermia contributed to development of respiratory distress in most of the neonates (81%) as short-term outcome where it had limited effects on the long-term outcome of the neonates.

The present study which only included hypothermic neonates, 60% of neonates had mild hypothermia (36.0-36.5°C) and remaining had moderate hypothermia (32.0-35.9°C). None of the neonates had severe hypothermia (<32°C). A similar study on 341 infants was conducted where 79 neonates (23%) were normothermic, 100 (29%) had mild hypothermia, 162 (48%) had moderate hypothermia [21]. A cohort study of 8782 infants was conducted where mean admission temperature was 36.3°C; 30.5% were mildly hypothermic, 25.6% were moderately hypothermic, 0.1% were severely hypothermic, 43.0% were normothermic [11].

In this study, 81% of hypothermic neonates suffered from RDS which was the most common co-morbidity followed by sepsis (22.2%). This finding is in line with the findings from a study conducted in China which found that out of 546 cases of moderate to severe hypothermia, 453 (82.9%) neonates had RDS which decreased to 404 neonates out of 554 (72.9%) admitted with mild hypothermia [13]. This is in stark contrast with a study conducted in in Malawi which found that two most common comorbidities were RDS (38%) and transient tachypnoea of the newborn (23%) where normothermic neonates were taken into account [22].

A study on Korean neonates found that out of 3464 neonates who were having some degree of hypothermia, 798 neonates suffered from sepsis which accounted for 22.83% of hypothermic neonates [23]. A different study by Chang HY et al., reported sepsis in 10 (10%) of neonates with mild hypothermia and 27 (16.7%) neonates with moderate hypothermia [21]. The present study also reflects a similar finding. Forty-two neonates suffered from sepsis which accounted for 22% of neonates with hypothermia. In the present study, sepsis was second most common short-term outcome among the neonates admitted with admission hypothermia.

In the present study, IVH most commonly occurred in the preterm neonates. IVH did not occur at the time of birth but it developed in the first few days of the life. A total of five newborn were detected with IVH out of which one did not survive. All five newborn with IVH were in the moderate category of hypothermia. Out of five, two were below the 28 weeks of gestation and rest three were between 28-34 weeks of gestation. Chang H-Y et al., also reported the higher chances of developing IVH in the preterm and low-birth weight neonates [21]. They also reported that moderate hypothermia was associated with IVH in the neonates. Miller SS et al., also reported a significant association between moderate hypothermia and IVH [11].

A high likelihood of RDS, IVH and Late-Onset Neonatal Sepsis (LOS), advanced retinopathy of prematurity was found in neonates with admission hypothermia [13,14]. In the present study, most common (81%) short-term outcome reported was RDS.

In this study, development assessment was done at 12 months of age using DAS II scale on 170 neonates who came for follow-up for a period of one year. It was found that mean developmental age and mean developmental quotient were in normal range at 12 months of age. No long-term visual impairment was seen in 170 neonates who came for follow-up for a period of one year. Chang HY et al., concluded that admission hypothermia was associated with higher RDS and mortality rates but it plays a limited role among the multi-factorial causes of neurodevelopmental impairment [21].

Limitation(s)

The finding of this study has to be seen in light of some limitations like it could not address how well certain interventions were performed, such as drying the baby after birth, wrapping with warm/clean clothing during delivery, or quality and duration of skin-to-skin contact, all of which are factors which have high potential to prevent neonatal hypothermia. There was lack of data about normothermic neonates and their short and long-term outcome. Certain hospital-related factors like the skills and qualifications of the health care providers working in the delivery rooms as well as in the NICUs which might have associated with the outcome of the neonates could not be addressed.

CONCLUSION(S)

Neonates require a neutral thermal surrounding for their optimal growth and development. The result of this observational study

demonstrates that the most common form of hypothermia among neonates is mild hypothermia. Severe hypothermia in neonates is rare. Among the short-term outcome, RDS constituted the biggest percentage of neonatal morbidity and neonatal mortality followed by sepsis. RDS was seen in all hypothermic neonates who were extremely preterm. Gestational age of neonate carried a significant relationship with the outcome in terms of developing co-morbidities and their survivability. The observations showed that mild and moderate admission hypothermia play a limited role in long-term neuro-developmental outcome.

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