Original Article

Effect of Elevated Temperature on Immediate Neurodevelopmental Outcome in Term Neonates with Hypoxic-Ischemic Encephalopathy

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Abstract

***Background**: Among term infants, hypoxic-ischemic encephalopathy due to acute perinatal asphyxia remains an important cause of neurodevelopmental deficits in childhood. Treatment is currently limited to supportive intensive care, without any specific brain-oriented therapy.* ***Objective**: To determine whether the risk of death or moderate/severe neurodevelopmental impairment in term infants with hypoxic-ischemic encephalopathy increases with relatively high skin or rectal temperature between 12 and 72 hours of birth.* ***Materials and Methods**: This was a prospective observational study. Asphyxiated newborns who came within 12 hours of birth were enrolled in this study. Both axillary and rectal temperature were recorded 6 hourly for 72 hours and each infant`s temperature for each site were rank ordered. Then mean of all axillary and rectal temperatures of each neonate was calculated. Outcomes were related to temperatures in logistic regression analyses for the elevated/relatively high temperatures and normal/low temperatures group, with adjustment of the level of encephalopathy and gender.* ***Results**: The mean axillary temperature was 36.07 ± 6.1^{0}C and in 25.71%, 11.92% and 6.32% cases axillary temperatures were >37^{0}C, >37.5^{0}C and >38^{0}C respectively. The mean rectal temperature was 36.8 ± 6^{0}C, and in 43.53%, 30.02% and 19.97% cases rectal temperatures were >37^{0}C, >37.5^{0}C and >38^{0}C respectively. Mean ambient temperature was 26.17^{0}C. There was significant correlation between axillary and rectal temperatures (r=0.889). For elevated temperature, the odds of death or moderate to severe impairment increased 8.9-fold (CI 0.906–88.18) and the odds of death alone increased 4.6-fold (CI 0.373–56.83). The odds of impairment increased 1.84-fold (CI 0.45–7.50).* ***Conclusion**: Relatively high temperature during usual care after hypoxic-ischemia in term neonates was associated with adverse neurodevelopmental outcomes.*

***Key words**: Hypoxic-ischemic encephalopathy (HIE); Neurodevelopmental outcome; Temperature; Term neonate; Developmental domain; Neonatal intensive care unit*

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Introduction

Perinatal asphyxial encephalopathy is associated with high morbidity and mortality rates worldwide and is a major burden for the patient, the family, and society. Hypoxic-ischemic encephalopathy (HIE) in term infants occurs at a rate of about three per thousand live-born neonates in developed countries, but the rate is estimated to be higher in the developing world.[1-2] Physicians who care for these children in the period after injury have traditionally provided supportive care with little expectation that their interventions would salvage brain tissue or have an effect on the final outcome. This approach is changing with the recognition that brain temperature during and/or after hypoxia-ischemia may modulate the extent of injury.[3]

Experimentally, reducing body temperature by 3−5°C below the normal level reduces cerebral injury and improves neurologic function after asphyxia.[4-9] Conversely, small increases in brain temperature in neonatal animals during and/or after hypoxia-ischemia increase the extent of injury.[10,11]

Most infants at a neonatal intensive care unit (NICU) have a decreased ability to maintain a neutral core temperature. An abnormal core temperature is associated with enhanced risk of mortality and morbidity and therefore needs to be monitored.[12] Few studies mentioned elevated temperature as a risk factor for adverse outcomes. Still there is insufficient data how and up to what extent temperature affects the neurodevelopmental outcome of HIE infants. So this study will help us to know if elevated or relatively high temperature is a risk factor for adverse neurodevelopmental outcome in term neonates with HIE.

Materials and Methods

This prospective observational study was conducted in the Department of Neonatal Intensive Care Unit (NICU), Dhaka Medical College Hospital, Dhaka during the period July 2016 to June 2017. Total sample size was 60. All the admitted term newborns who came within 12 hours of birth with history of perinatal asphyxia having features of hypoxic-ischemic encephalopathy were included in this study. Detailed history was taken and thorough physical examination of the newborn was carried out and findings were noted on the questionnaire. Newborns presenting with IUGR, congenital malformation and who developed other illness like septicemia, pneumonia, meningitis during admission were excluded from the study.

Neonates were treated according to standard protocol of the institution. Axillary and rectal temperatures of each patient were recorded on admission and thereafter 6 hourly for 72 hours. Axillary temperature was recorded by a mercury thermometer and rectal temperature by a glass rectal thermometer. Ambient temperature was also recorded by an ambient thermometer. Each neonate's temperatures for each site were rank-ordered. For each neonate 12 axillary and 12 rectal temperatures were plotted. Then mean of all axillary and rectal temperature of each neonate was calculated. Here rectal temperature was used for data analysis. Rectal temperature >37^0 C was defined as elevated/relatively high temperature. Outcomes were related to temperatures in logistic regression analyses for the elevated temperatures and normal/low temperatures group. Blood specimens were taken at admission for complete blood count, serum electrolyte, CRP, ABG. All the blood specimens were tested by the same procedure. At discharge and 3 months after discharge neurodevelopmental assessment were done by a Developmental therapist using RNDA[13] tools for neonates. Intervention (developmental therapy and stimulation) was given to each neonate at discharge and also at 3 months. All the findings were noted in the case collection sheet.

Results

The study included 60 neonates suffering from hypoxic-ischemic encephalopathy of different stages and treated in Neonatal ICU of Dhaka Shishu Hospital and Dhaka Medical College Hospital. Among them 37 (61.7%) were male and 23 (38.3%) were female, mean age at enrollment was 6.42 ± 4.38 hours, mean weight 2813 ± 387 gm, mean length 50.45 ± 1.47 cm and mean OFC was 33.63 ± 1.2 cm. Gestational age on enrollment was 38.73 ± 1.03 weeks (Table I).

Among 60 neonates, 33.33% (n=20) was in stage I, 40% (n=24) was in stage II and 26.67% (n=16) was in stage III of hypoxic-ischemic encephalopathy. In neonates having HIE stage I, 30% (n=18) had normal or low temperature. Neonates who developed HIE stage III mostly 23.3% (n=14) had relatively high or elevated temperature (Table II).

Among enrolled neonates, the mean axillary temperature was 36.07 ± 6.1^{0}C. In 25.71%, 11.92% and 6.32% cases temperatures were >37^{0}C, >37.5^{0}C and >38^{0}C respectively. The mean rectal temperature was 36.8 ± 6^{0}C. In 43.53%, 30.02% and 19.97% cases temperatures were >37^{0}C, >37.5^{0}C and >38^{0}C respectively (Table III). The r value between axillary and rectal temperature was 0.889. There was significant correlation between axillary and rectal temperature (Fig 1).

Among enrolled neonates, 20% (12) died before discharge. On neurodevelopmental assessment, 11.67% (7) neonate had normal development whereas development was mild, moderate and severely impaired in 10% (6), 33.33% (20) and 20% (15) cases respectively (Fig 2). Outcome was also measured in specific domains along with its severity (Table IV).

Logistic regression analyses relating elevated/relatively high temperature to the early neurodevelopmental outcome indicated significant association. For elevated temperature, the odds of death or moderate to severe impairment increased 8.9-fold (CI 0.906–88.18) and the odds of death alone were increased 4.6-fold (CI 0.373–56.83). The odds of impairment were increased 1.84-fold (CI 0.45–7.50) (Table V). Among 48 neonates, 40 infants came after three months for follow-up. Logistic regression analyses relating rectal temperature to the early neurodevelopmental outcome in individual domain indicated significant association for relatively high/ elevated temperature (Table VI).

Table I: Clinical characteristics of newborns on enrollment (N=60)

Characteristics	Mean ± SD
Age (hours)	6.42 ± 4.38
Weight (gm)	2813 ± 387
Length (cm)	50.45 ± 1.47
OFC (cm)	33.63 ± 1.2
Gestational age (weeks)	38.73 ± 1.03

Table II: HIE stages of studied population (N=60)

HIE staging	Hypothermia/Normal temperature Number (%)	Relatively high/Elevated temperature Number (%)
I	18 (30)	2 (3.3)
II	13 (21.7)	11 (18.3)
III	2 (3.3)	14 (23.3)

Table III: Mean and percentage of recorded temperatures

Characters	Axillary temperature	Rectal temperature	Ambient temperature
Mean temperature	36.07 ± 6.1^{0}C	36.8^{0}C ± 6^{0}C	26.17^{0}C
Median temperature	36^{0}C	36.7^{0}C	26^{0}C
Temperature >37^{0}C	25.71%	43.53%	
Temperature >37.5^{0}C	11.92%	30.02%	
Temperature >38^{0}C	6.32%	19.97%	

Table IV: Neurodevelopmental outcome at discharge in specific domains (n=48)

Domains	Normal Number (%)	Mild Number (%)	Moderate Number (%)	Severe Number (%)
Primitive reflex	13 (27.1)	19 (39.6)	9 (18.8)	7 (14.6)
Gross motor	17 (35.4)	15 (31.2)	11 (22.9)	5 (10.4)
Fine motor	40 (83.3)	4 (8.3)	4 (8.3)	0
Vision	35 (72.9)	3 (6.2)	8 (16.7)	2 (4.2)
Hearing	40 (83.3)	3 (6.2)	1 (2.1)	4 (8.3)
Speech	28 (58.3)	2 (4.2)	7 (14.6)	11 (22.9)
Cognition	33 (68.8)	4 (8.3)	7 (14.6)	4 (8.3)
Behavior	28 (58.3)	10 (20.8)	4 (8.3)	6 (12.5)
Seizure	26 (54.2)	4 (8.3)	8 (16.7)	10 (20.8)

Table V: ORs relating rectal temperature to adverse outcomes at discharge

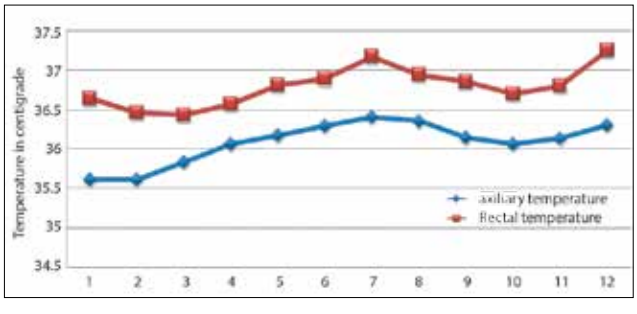
Outcome	Adjusted ORs*	Confidence Interval	p values
Death or moderate to severe impairment	8.93 (S)	0.906–88.18	0.061
Death	4.6 (S)	0.373–56.83	0.233
Impairment	1.84 (S)	0.45–7.50	0.39

*Adjusted for level of encephalopathy and gender
ORs >1 significant

Table VI: ORs relating rectal temperature to adverse outcomes at 3 months in specific domains

Domains	ORs	Confidence Interval
Primitive reflex	2.20	0.622–7.78
Gross motor	2.27	0.53–9.69
Fine motor	2.33	0.65–8.31
Vision	1.97	0.49–7.83
Hearing	4.39	0.89–21.56
Speech	1.48	0.43–5.06
Cognition	2.28	0.80–9.5
Behavior	3.66	1.04–12.90
Seizure	6.94	1.75–27.41

ORs >1 significant



1st 24 hours 2nd 24 hours 3rd 24 hours

Fig 1. Correlation between mean axillary and mean rectal temperature

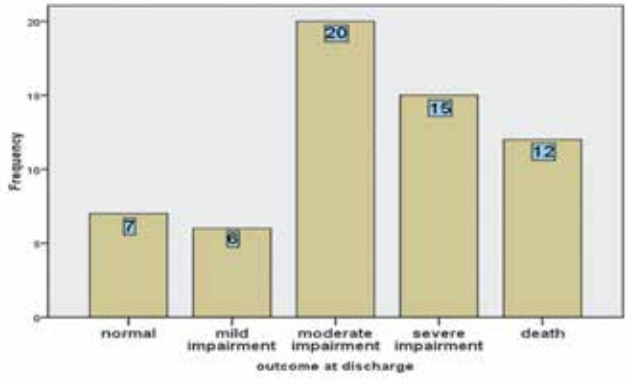


Fig 2. Neurodevelopmental outcome at discharge

Discussion

At and 3 months of discharge neurodevelopmental outcome was assessed using rapid neurodevelopmental assessment (RNDA)[13] tools for neonates. The tools were validated against the Baley scale for infant development where mental developmental index (MDI), psychological developmental index (PDI) and behavioral rating index (BRI) are correlated with the RNDA findings. This is the first research work in Bangladesh measuring neurodevelopmental outcome in relation to temperature. The study results and comparison with other study findings will help to evaluate the real estimation.

Thermal regulation seems to be an important factor determining neurodevelopmental outcome. Immediately after delivery, if no action is taken, the core and skin temperatures of a term neonate can decrease at a rate of approximately 0.1°C and 0.3°C per minute respectively.[14] The World Health Organization defines mild hypothermia as a core body temperature of 36°–36.4°C, moderate hypothermia as 32°−35.9°C and severe hypothermia as less than 32°C.[15] The rapid decline in temperature is mainly due to physical characteristics of the newborn and environmental factors of the delivery area. The newborn immediately loses heat by evaporation, convection, conduction and radiation, dependent on the ambient air pressure, temperature and humidity and the temperature of surrounding surfaces.[16,17]

In this study, neonates with HIE-III mostly had relatively high/elevated temperature. Whereas neonates with HIE-I had the opposite. In a study by Laptook et al[18], the mean core temperature was found 37.2 ± 0.7°C over the 72-hour period, and in 63%, 22%, and 8% cases temperatures are >37°C, >37.5°C, and >38°C, respectively. The mean skin temperature is 36.5 ± 0.8°C, and in 12%, 5%, and 2% cases temperatures are >37°C, >37.5°C, and >38°C respectively. Core temperature is relatively higher than in our study. Those findings may be due to using of oesophageal probe to measure core temperature.

Among enrolled neonates, 20% (12) died before discharge. Qureshi et al[19] and Shireen et al[20] found 15% and 16% death following HIE after hospitalization. In this study, on neurodevelopmental assessment, 11.67% (7) neonate had normal development whereas development was mild, moderate and severely impaired in 10% (6), 33.33% (20) and 20% (15) neonates respectively. These findings are consistent with the findings of a study done by Selina et al[21] in ICH and SSF Hospital, Mirpur, Dhaka. In another study done by Khan et al[22] among preterm infants in Bangladesh, normal development is observed in 32%, mild impairments are found in 45%, and serious impairments are found in 23% of preterm infants.

This study labelled the impairment at different domains. At discharge, RNDA was done in 48 neonates. In this study, majority neonates had impairment in primitive reflex and gross motor domain. But the severely impaired domains were seizure, speech, behavior, primitive reflex and gross motor. These results are consistent with a previous study.[23]

In this observational study, broad ranges of axillary and rectal temperature were observed among neonates who were getting usual treatment in NICU. Within this range, relatively high rectal temperature was associated with increase in the odds of death, death or moderate to severe impairment and impairment alone in analyses controlling for the degree of encephalopathy and gender. A study done by Laptook et al[18] demonstrated an association between elevated temperature and death or moderate/severe disability. The association could be attributable to the severity of the brain lesion, specific adverse effects of an elevated temperature, or both. They found that the risk of death or moderate/severe disability was increased 3.6-fold to four-fold for every 1°C increase in the mean of the highest quartile of skin or esophageal temperature. The risk of death alone increased 5.9-fold for every 1°C increase in the median esophageal temperature.

After 3 months of discharge, 40 (83.33%) infants came for follow-up. Regression analyses relating rectal temperature to the neurodevelopmental outcome at 3 months in each domain indicated significant associations for relatively high/elevated temperature. But no data were found relating temperature to neurodevelopmental outcome in multiple developmental domains.

Relatively high temperature during usual care after hypoxic-ischemia in term neonates was associated with adverse neurodevelopmental outcomes. These results may reflect underlying brain injury and/or adverse effects of temperature on immediate outcomes. This study demonstrated that a significant proportion of term neonates with HIE developed NDIs. Not only motor function but also cognition, behavior, seizure, hearing and vision were impaired significantly.

Relatively high temperature was also associated with adverse NDIs in multiple developmental domains.

Unnecessary warming of newborns has to be prevented both in home and hospital settings. Outcome should be measured in each newborn with HIE and intervention with developmental therapy and stimulation should be provided for every child. A randomized, controlled trial would be needed to determine whether the prevention of elevated temperature would reduce the rates of death or moderate/severe disability in term neonates with HIE.

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