Original Article

Body Temperature Trends during Passive Hypothermia in Infants with Severe Perinatal Hypoxic-Ischemic Encephalopathy: A Single-Center Study in Thailand

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Background: Therapeutic hypothermia is a standard treatment in infants with moderate or severe perinatal hypoxic-ischemic encephalopathy (HIE). Passive hypothermia (PH) is initiated immediately after birth resuscitation and is continued during transfer to the neonatal intensive care unit (NICU). Information regarding the effectiveness of PH in severe HIE infants in the tropics are scarce.

Objective: To investigate body temperature (BT) trends in infants with severe perinatal HIE who received PH after birth resuscitation and during transfer to the NICU in Thailand.

Materials and Methods: The present prospective descriptive study was conducted at Siriraj Hospital, Thailand's largest national tertiary referral center. PH was commenced in the delivery room in HIE infants that had no contraindications for therapeutic hypothermia. Continuous rectal temperature was monitored from post-resuscitation until NICU admission. BT trend and proportion of infants who reached therapeutic range were observed.

Results: Ten infants had PH commenced in the delivery suite between 2015 and 2018. Mean ± standard deviation birthweight was 2,752.1±70.3 grams. All infants had severe HIE that required intubation during birth resuscitation. Median (min, max) age at PH initiation was 55.0 (7, 343) minutes, and median duration of PH was 42.5 (10, 165) minutes. Mean BT upon NICU admission was 35.9±0.7°C. Seven infants had BT of less than 36.5°C, but none reached therapeutic range (33.0°C to 34.0°C). BT was significantly lower at NICU admission than at PH initiation (p=0.01). Correlation coefficient between change in BT and duration of PH was 0.5 (p=0.11). No adverse cardiovascular events were observed during PH.

Conclusion: Although 70% of study infants were hypothermic (less than 36.5°C) by the time they were admitted to the NICU, PH therapy was ineffective for inducing hypothermia to within therapeutic range (33.0°C to 34.0°C) in infants with severe perinatal HIE. A detailed written protocol, an experienced team, and appropriate monitoring devices are recommended when therapeutic hypothermia is indicated in this vulnerable patient population.

Keywords: Body temperature trends, Passive hypothermia, Infants, Severe perinatal hypoxic-ischemic encephalopathy

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Therapeutic hypothermia (TH) was reported to be effective for decreasing mortality and cerebral palsy in term infants who had moderate to severe perinatal hypoxic-ischemic encephalopathy (HIE)[1]. Therefore, TH is provided as a standard of care in settings where the appropriate resources are available. Several studies have investigated TH to maximize the therapeutic effect of the therapy, and to lower the potential for side effects. The findings of animal and human studies provided the basis for the recommendation that TH must be initiated within six hours of life. The timing of onset of hypoxic-ischemic (HI) injury is difficult to identify since it usually occurs in utero. Retrospective studies reported better outcomes in patients who had

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earlier initiation of TH[2,3]. Several studies revealed the current preference for initiating therapy immediately after birth, and continuing therapy during transport to the neonatal intensive care unit (NICU)[4-9]. The methods used to induce hypothermia included natural hypothermia (passive hypothermia), portable servo-controlled device, fan, and application of cold surface material on the skin, such as cold pack, phase-changing material, or water-filled bag.

Passive hypothermia (PH) is an affordable option in resource-limited settings where a portable servo-controlled cooling device is not available[10]. PH is a TH method that is defined as passive lowering of body temperature (BT) with no active intervention to accelerate the speed of hypothermia onset, to further decrease the patient's BT, or to promote rewarming. Thermal control requires an intact and properly functioning central nervous system (CNS)[11]. Thermogenesis in newly born infants requires metabolism of brown fat, body movement, and an intact autonomic nervous system (ANS) to control capillary tone. Infants with significant HIE are at high risk for developing malfunctions of heat generation mechanisms, which can lead to rapid onset of hypothermia. Moreover, infants with moderate or severe HIE are more likely to have unobstructed heat loss into the environment. Changes in BT depend primarily on environmental temperature and ability to create endogenous heat. The effectiveness of PH depends on HIE severity, duration, and environmental temperature. Studies in PH reported a range of BTs upon NICU admission. However, the target range in TH is 33.0°C to 34.0°C. A study from Australia reported a rate of undercooling (greater than 34.0°C) of 24%, while 10% of infants had overcooling (less than 33.0°C)[12].

Most previous studies were conducted in countries located in non-tropical climates. Data relating to the effectiveness of PH for inducing hypothermia into therapeutic range in severe perinatal HIE cases in tropical regions are scarce. Accordingly, the aim of the present study was to investigate BT trends in infants with severe perinatal HIE who received PH after birth resuscitation and during transfer to the NICU in Thailand.

Materials and Methods

The present study was a single-center, prospective, descriptive study, conducted at Siriraj Hospital, Mahidol University, Bangkok, Thailand between 2015 and 2018. Whole-body TH (targeted temperature range between 33.0°C and 34.0°C) for moderate or severe perinatal HIE infants with gestational age of at least 35 weeks was instituted at the present study center in 2012. A PH protocol was then developed and had been used in the delivery room since 2015. All birth resuscitation steps at the present center were and continued to be in accordance with standard neonatal resuscitation guidelines (ILCOR 2010 and 2016), including resuscitation under prewarmed radiant warmer and the use of warm and dry towels. The temperature of the resuscitation room was set at 25°C throughout the study period. Following respiratory and cardiovascular stabilization, infants were evaluated for eligibility to receive TH. Infants who had uncertain diagnosis or severity of encephalopathy were stabilized under routine thermal control between 36.5°C and 37.5°C. If deemed eligible, PH was initiated by turning off the radiant warmer and uncovering the baby. The transport incubator was also turned off and all of the windows were opened. Needed gases were supplied without heated humidification for all types of ventilation support. Patient monitoring included continuous cardiac, peripheral oxygen saturation, and rectal temperature monitoring. All parameters were monitored using a portable transport monitor (IntelliVue MP2, Philips, USA)

Statistical analysis

SPSS Statistics v.18.0 (SPSS Inc., Chicago, IL, USA) was used to perform all data analyses. Number and percentage were used to describe categorical variables, and mean ± standard deviation or median (minimum, maximum) was used to show continuous variables. Difference in BT between time of commencing PH and NICU admission was analyzed using paired t-test. Pearson's correlation coefficient (r) was employed to investigate for correlation between changes in BT and duration of PH. A p-value less than 0.05 indicated statistical significance.

Results

Ten asphyxiated infants that received PH in the delivery suite between 2015 and 2018 were included. The mean birth weight and gestational age were 2,752.1±670.3 grams and 36.7±2.3 weeks, respectively. Four infants were in the low birth weight group (less than 2,500 g). All infants had severe HIE and were intubated during resuscitation. The median (min, max) Apgar score was 1 (1, 3) and 2 (1, 4) at 1 minute and 5 minutes, respectively. Mean umbilical arterial (UA) pH was 6.9±0.1. The median (min, max) age of commencing PH and median duration of PH was 55.0 (7, 343) minutes and 42.5 (10, 165) minutes,

Table 1. Individual infant characteristics, birth resuscitation and passive hypothermia therapy details (n=10)

Case No.	GA (weeks)	BW (g)	BW-GA status	Apgar score			Birth resuscitation	Cord A		Cord V		Passive hypothermia	
				1-minute	5-minute	10-minute		pH	BD	pH	BD	Age at initiation (minute)	Duration (minute)
1	37	3,160	AGA	2	4	5	Intubation	6.91	10.60	6.93	12.70	54	45
2	39	4,310	LGA	1	1	3	Intubation CC Epi	6.77	17.50	6.90	18.30	56	60
3	40	2,480	SGA	3	4	7	Intubation	6.85	14.20	7.17	9.20	7	165
4	38	2,800	AGA	2	2	5	Intubation	6.71	21.10	6.76	21.5	81	60
5	36	2,430	AGA	1	1	1	Intubation CC Epi	6.89	25.30	6.95	18.70	100	40
6	35	2,500	AGA	1	1	1	Intubation CC Epi	6.88	17.70	6.86	18.80	48	50
7	36	2,560	AGA	1	2	3	Intubation	6.84	24.80	7.31	5.80	101	30
8	39	3,110	AGA	1	2	3	Intubation CC	7.07	19.20	7.25	6.30	49	20
9	33	1,810	AGA	1	3	5	Intubation	6.91	19.50	7.17	11.20	343	25
10	34	2,360	AGA	1	4	6	Intubation	N/A	N/A	N/A	N/A	26	10

AGA=appropriate-for-gestational age; BD=base deficit (mmol/L); BW=birth weight; CC=chest compression; Cord A=umbilical arterial blood gas analysis; Cord V=umbilical venous blood gas analysis; Epi=epinephrine infusion; GA=gestational age; LGA=large-for-gestational age; N/A=not available; SGA=small-for-gestational age

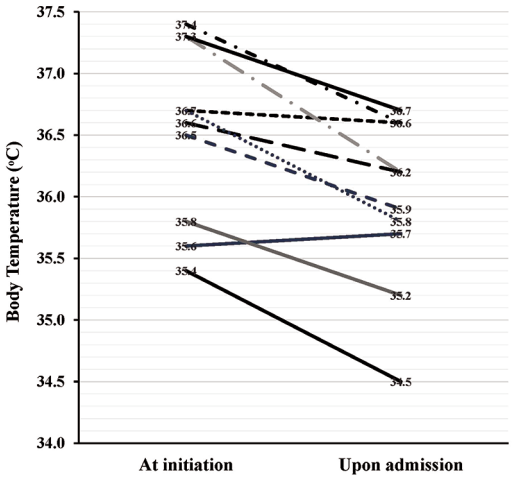

Figure 1. Temperature changes during passive hypothermia between passive hypothermia initiation and NICU admission for each included infant (n=10).

respectively. Individual infant characteristics and birth resuscitation details are shown in Table 1. The mean BT at initiation of PH and at NICU admission was 36.5±0.7°C and 35.9±0.7°C, respectively. Seven infants had NICU admission BT less than 36.5°C. No adverse respiratory or cardiovascular events were observed during transport in any infants.

A significant decrease in BT from initiation of PH to NICU admission was observed, with a mean decrease of 0.6±0.4°C, (p=0.001). The mean rate of BT decrease was 0.02±0.02°C per minute. BT changes from PH initiation to NICU admission are shown in Figure 1. Correlation coefficient between change in BT and duration of PH was 0.5 (p=0.1).

Discussion

In the present study, the authors investigated the effect of PH on BT in severely asphyxiated infants at a major university-based medical center located in the tropics. The temperature in the present setting ranges from relatively cold in the delivery room to warm outside. Some studies reported lowering of BT to therapeutic range during transfer with PH, and particularly in severe cases[13-15]; however, none of the infants in the present study were able to achieve the target range of TH (33.0°C to 34.0°C) when being cooled by PH. Nevertheless, mean BT upon NICU admission was significantly lower than at initiation,

and a majority (70%) of infants were cooled to within hypothermic range (less than 36.5°C). Animal study revealed the neuroprotective effect of lowered BT despite not reaching the target temperature[16]. However, hypothermia increases both energy expenditure and pulmonary vasoconstriction, which are likely to burden transitional circulation, particularly in infants with significant perinatal asphyxia, which may further impede the stability of cardiovascular function[11]. A study in PH during transport observed a substantial proportion of either overcooling or undercooling upon arrival at the cooling center[12]. Therefore, clinicians must continuously monitor and observe for changes in BT, a written protocol must be developed and implemented to monitor for possible side effects secondary to hypothermia, and a management plan during therapy is recommended[17,18]. Since the present results revealed BT that failed to reach the target therapeutic range, and no statistically significant correlation was found between duration of PH and change in BT, the authors were unable to predict the rate of temperature change. Therefore, the authors recommend continuous and accurate temperature and cardiovascular monitoring during therapy.

During the study period, the delivery room temperature was set to the temperature recommended in the ILCOR guideline. As such, infants were exposed to temperature variations only during transfer to the NICU. Therefore, the authors concluded that the uncontrolled temperature of the environment outside of the delivery room influenced the effectiveness of PH. Moreover, the association between hyperthermia and severe brain damage is well established[19]. In resource-limited settings where TH may not be available, caregivers need to initiate other neuroprotection interventions to prevent hyperthermia during stabilization and while preparing for transfer to the cooling center. The present institutional incidence of hyperthermia (BT over 37.5°C) upon NICU admission in any high-risk term infants was 7%, which is higher than the 4.7% of infants admitted with hypothermia (unpublished data). Therefore, in conditions like moderate to severe HIE associated with a high risk of brain injury, meticulous thermal control is required via continuous monitoring with an appropriate temperature monitoring device. The authors also recommend the use of a servo controlled cooling device for transport, or the air-controlled mode of a transport incubator with a relatively low preset temperature as opposed to the use of PH when TH is indicated[14].

The findings of the present study should be generalized to other settings cautiously. First, the very small number of studied infants were insufficient for statistical power to identify significant associations to facilitate the development of a protocol that could predictably reduce BT to within therapeutic range. The relative rarity of moderate to severe HIE suggests the need for a multi-center research effort. Second, all of the infants in the present study had severe HIE. As such, no aspect of the present data or findings should be extrapolated to infants with mild or moderate HIE, because the dynamics of BT change in these two sub-groups may be different from those of severe HIE. Small number of infants and only severe HIE infants were included because the responsible physician needed to ensure eligibility for TH. Clinical diagnosis alone during very early life may change within the next few hours of life. Therefore, clinical assessment for encephalopathy must be reassessed by an experienced clinician before initiating TH. Lastly, since the authors applied PH to inborn infants only due to the availability of experienced team and instrument, the duration of PH was relatively short. Time spent in PH ranged from 10 to 165 minutes and depended upon certain inclusion criteria and availability of NICU beds. Given the observed trend toward lowered BT in all studied infants despite the relatively short duration of PH, it is possible that the target therapeutic range could be achieved or infants could even develop overcooling in situations or settings where the transfer time is longer. This supports the authors' recommendation regarding the importance of a written protocol, experienced team, and accurate and appropriate monitoring devices. In situations and settings that lack these suggested support mechanisms, the authors recommend to not initiating PH. The alternative strategy should be active prevention of hyperthermia via continuous or frequent temperature measurements during post-resuscitation and during transfer.

Conclusion

Although 70% of study infants were hypothermic (less than 36.5°C) by the time they were admitted to the NICU, PH therapy was ineffective for inducing hypothermia to within therapeutic range (33.0°C to 34.0°C) in infants with severe perinatal HIE. A detailed written protocol, an experienced team, and appropriate monitoring devices are recommended when TH is indicated in this vulnerable patient population.

What is already known on this topic?

- TH is effective for decreasing mortality or

cerebral palsy in term infants who had moderate to severe perinatal HIE when it was initiated within six hours of life.

• PH has been adopted widely to commence the therapy within the window period.

What this study adds?

• Majority of infants with severe perinatal HIE who received PH after birth resuscitation and during transfer to the NICU were hypothermia.

• In tropical climate environment, PH therapy was ineffective for inducing hypothermia to within therapeutic range.

Conflicts of interest

The authors declare no conflict of interest.

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