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Phenobarbital and temperature profile during hypothermia for hypoxic-ischemic encephalopathy

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Conflict of Interest

Authors disclose no commercial, financial, or other associations that could pose a conflict of interest in connection with the submitted article.

Ethical approval

This was a secondary analysis of the Eunice Kennedy Shriver National Institute of Child Health and Human Development (NICHD) Neonatal Research Network Whole Body Hypothermia Trial. The trial was performed after informed consent was obtained.

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Abstract

Data from the whole body hypothermia trial was analyzed to examine the effects of phenobarbital administration prior to cooling (+PB) on the esophageal temperature (Te) profile, during the induction phase of hypothermia. A total of 98 infants were analyzed. At enrollment, +PB infants had a higher rate of severe HIE and clinical seizures and lower Te and cord pH than infants that have not received PB (−PB). There was a significant effect of PB itself and an interaction between PB and time in the Te profile. Mean Te in the +PB group was lower than in the −PB group and the differences decreased over time. In +PB infants the time to surpass target Te of 33.5°C and to reach the minimum Te during overshoot were shorter. In conclusion, the administration of PB prior to cooling was associated with changes that may reflect a reduced thermogenic response associated with barbiturates.

Keywords

phenobarbital; hypoxic-ischemic encephalopathy; hypothermia; temperature control

Introduction

The use of therapeutic hypothermia is very likely increasing over the last 5 years, since publications of six randomized controlled trials and a meta-analysis showed that therapeutic hypothermia in newborns with hypoxic-ischemic encephalopathy is safe and significantly reduces both death and disability. [1–6] In these trials, hypothermia was induced and maintained by active cooling and the initial temperature applied to the infants was well below thermoneutrality. The average time to achieve the target temperature was between 1–2 hours, which raises the possibility that some infants responded to cooling with an initial increase in heat production, or thermogenesis. In fact, a thermogenic response to cooling is characteristic of all homeotherms, is rapidly triggered after birth and may result in increases in oxygen consumption by about 34% in a healthy newborn exposed to an ambient temperature of 26°C. [7–9] Although asphyxiated infants have a decreased body temperature (Tb) during the first hours after birth, the thermogenic response of these infants to lower ambient temperatures has not been investigated. [10]

After a hypoxic ischemic insult, clinical seizures have been reported in 43 to 59% of infants before initiation of hypothermia. [1–3] In the setting of neonatal encephalopathy secondary to hypoxia-ischemia, seizures are commonly treated with phenobarbital (PB). [11,12] Effective plasma concentrations of PB can be achieved within 10 min after a loading dose of 15mg/kg [13,14] and barbiturates can substantially reduce brain metabolic rates at doses that are 10 to 20% of the usual anesthetic doses and decrease thermogenesis. [15] Therefore, the administration of phenobarbital to infants undergoing therapeutic hypothermia may modify their core temperature profile during the induction phase due to its effect on brain metabolic rate (BMR) and thermogenesis.

In the NICHD whole body cooling trial the temperature profile of the neonates undergoing therapeutic hypothermia for hypoxic-ischemic encephalopathy has been characterized.[16]

The induction phase of cooling is defined as the time from initiation of cooling to equilibration of target core temperature. Since a significant number of infants undergoing body cooling received PB for seizures (either treatment or prophylaxis) as part of usual care in the participating centers, and cooling on transport was not part of the trial, it provided the opportunity to examine the effects of PB administration on the profile of temperature changes during this phase of the hypothermic treatment. This is important because careful management of Tb during induction, with the goal to prevent oscillations, overshoot and to achieve the target temperature safely and quickly may play a critical role in the effectiveness of this therapy. In this study, we hypothesized that there would be a more rapid and/or greater fall in esophageal temperature during the initiation of hypothermia among infants given PB prior to cooling when compared to infants that did not receive phenobarbital. This may reflect the effects of barbiturates on BMR and thermogenesis.

Methods

Study Infants

This was a secondary analysis of the Eunice Kennedy Shriver National Institute of Child Health and Human Development (NICHD) Neonatal Research Network Whole Body Hypothermia Trial.[2] The trial was performed after informed consent was obtained. Eligibility criteria for therapeutic hypothermia included gestational age of ≥ 36 weeks, postnatal age of ≤ 6 hours, and subsequent fulfillment of specific physiologic and/or clinical criteria (severe acidosis or an acute perinatal event, low Apgar scores, and need for ventilation), followed by demonstration of moderate/severe encephalopathy using the modified Sarnat criteria.

Infants included in this analysis were those who underwent hypothermia in the study and were grouped according to receipt of phenobarbital before initiation of cooling (+PB) or not (−PB). The information on lag time between PB administration and initiation of cooling was not available in the data bank. We used any dose of phenobarbital given before the initiation of the hypothermia to define +PB and −PB groups.

Hypothermic treatment

The methods used for therapeutic hypothermia was described in detail previously. [2] Briefly, infants in the hypothermia group had an esophageal probe inserted and were placed on an infant-size blanket (25 × 33 inches) that was precooled to 5°C (Blanketrol II Hyper-Hypothermia System, Cincinnati Sub-Zero®). The Blanketrol was used in the servo-controlled mode with a target esophageal temperature (Te) of 33.5°C. No external heat source was used during the cooling intervention. The cooling period lasted 72 hours and was followed by 6hr of rewarming. Abdominal-wall skin temperature was monitored with a skin probe. Esophageal and skin temperatures were monitored continuously and recorded every 15 minutes for the first 4 hours, every hour for the next 8 hours, and every 4 hours for the duration of cooling.

Outcomes

A thermogenic response is elicited immediately after the application of a cooling stimulus and any effect of barbiturates on this response would be expected to occur during the induction phase defined as from initiation of cooling to achievement of a stable target temperature. Thus, temperatures analyzed for this study were those evaluated during the induction phase. The primary outcome was the esophageal temperature profile during induction and the specific aim was to determine if the profile differed between +PB and −PB infants. Te profile was evaluated by comparing Te values at baseline and at 30, 45 and 60 minutes of cooling.

Secondary outcomes of interest were the time to first surpass 33.5°C (overshoot), time to reach minimum Te below 33.5°C (prior to equilibration), minimum Te below 33.5°C, and the time to stabilize Te at 33.5 °C (amount of time after overshoot required to bring Te within 0.1°C of the target, i.e., to the first Te ≥ 33.4°C after overshoot).

Group Characteristics

Baseline data used to characterize each group included gestational age, birth weight, Apgar score at 10 minutes, umbilical blood gas, and out-born status. Other variables collected at the time of randomization included clinical seizures, use of PB and other medications, stage of encephalopathy, and use of inotropes. EEG confirmation of seizures was not available as part of this trial.

Statistical Analysis

Demographic and descriptive characteristics of the two groups were compared using Wilcoxon Two-Sample tests for continuous variables and Fisher's exact test for comparisons of categorical variables. Results are presented as mean ± SD, median and interquartile range or percentages as appropriate. A longitudinal mixed model was used to evaluate differences in the trajectory of temperature profiles over time between +PB and −PB groups during the induction phase of cooling. This model was adjusted for changes over time, and also included gestational age, level of encephalopathy at randomization, and an interaction term between PB and time. Secondary outcomes were not adjusted since they were considered exploratory analyses.

Results

Data from 98 out of 102 infants randomized to the hypothermia arm of the study were analyzed since in three patients data on the use of PB was missing and one patient was not submitted to hypothermia. Baseline characteristics are summarized in Table 1. A total of 44 infants were given PB before cooling. These infants were predominantly outborn and hypothermia was initiated at 5.2 ± 1.2 hours of life (−PB 4.9 ± 1.1 hrs; p=0.18). At study enrollment, +PB infants had a significantly higher proportion of severe HIE and clinical seizures and had lower cord pH values when compared to −PB infants. There were no differences between the two groups in the use of other anticonvulsants, analgesics or inotropes prior to the initiation of cooling,

Primary Outcome

The temperature profile of infants in the +PB and −PB groups is illustrated in the Figure 1. The Te at the initiation of cooling were 36.3 ± 1.1 °C for +PB and 36.9 ± 0.8 °C for −PB (p=0.02). There was a significant effect of PB itself (p=0.0002) and a significant interaction between PB and time (p = 0.0033) in the temperature profile of the infants undergoing hypothermia. Specifically, the overall mean differences in temperature between the +PB and −PB groups were different with temperatures in the +PB group lower than those in the −PB group. These group adjusted mean differences decreased over time: baseline = 0.86 °C ± 0.22 (p=0.0002); 30 min = 0.58°C ± 0.23 (p = 0.009); 45 min = 0.45°C ± 0.24 (p = 0.06) and 60 min = 0.31°C ± 0.26 (p = 0.24).

Secondary Outcomes

The unadjusted analysis of the esophageal temperature profile is summarized in Table 2. In +PB infants the time to surpass 33.5°C (0.77 ± 0.39hr *vs* 0.99 ± 0.51hr, $p < 0.01$)) and to reach the minimum Te below 33.5°C (1.24 ± 1.15hr *vs* 1.43 ± 0.93hr, $p < 0.01$) were shorter

when compared to −PB infants. No significant differences were observed in the minimum temperature below the target or time to stabilize at target.

Discussion

In this study we were able to demonstrate that phenobarbital administration prior to cooling was associated with an altered temperature profile during the induction phase of whole body hypothermia. The esophageal temperatures of +PB infants were significantly lower than −PB infants which may reflect a reduced metabolic rate and thermogenic response associated with the use of barbiturates. Even though targeted temperature reductions may be achieved more accurately with newer servo controlled devices than what was used in the current study, the induction of any cold stress even for therapeutic purposes may trigger counter-regulatory processes that may offset putative neuroprotective effects of hypothermia. [17–19]

The differences in the baseline characteristics of the two groups such as extent of fetal acidemia, severity of encephalopathy, occurrence of clinical seizures and differences on esophageal temperature before initiation of cooling, may also have affected the control of Tb and thermogenesis and account for the differences found between +PB and −PB groups. In this section we will separately discuss these important variables.

Extent of fetal acidemia

Cold-induced thermogenesis is present in neonates immediately after birth.[9] Several studies have demonstrated that thermogenesis is decreased during hypoxia and asphyxia [8,20,21] but there are few data describing this response after restoration of oxygenation. Animals exposed to antenatal or postnatal hypoxia had reduced brown adipose tissue mass and thermogenin concentration but normal thermogenic response when exposed to cold after discontinuation of the hypoxic insult. [22,23] Term newborn infants born at high altitude have decreased thermogenic response but were able to increase metabolic rate when ambient temperature (Ta) was further decreased.[8] Therefore, we would expect a thermogenic response to cooling in both groups of infants in our study. However, +PB infants had lower cord pH when compared to the −PB infants, which may reflect a more severe perinatal insult. Whether the magnitude of the thermogenic response is modified by the severity of the perinatal insult has not been investigated and may have contributed to differences in the Tb trajectory of +PB and −PB infants.

Severity of encephalopathy and occurrence of clinical seizures

At study enrollment, the +PB group had a higher proportion of infants classified as severe HIE. Severity of HIE was based on neurological exam or the presence of clinical seizures, since EEG was not performed. Although there were no differences in Apgar scores at 10 min or base deficit the cord pH was lower in the +PB infants providing evidence of greater impairment of gas exchange and possibly a more severe perinatal event. Therefore, the +PB group of infants were presumably exposed to a more severe brain insult and although we adjusted our model for the level of encephalopathy, a direct effect of severe brain injury upon thermogenesis may have affected the Tb profile during the induction phase. Animal studies have showed that even severely asphyxiated piglets [23] or decorticated rats [24] were able to elicit a significant thermogenic response when exposed to moderate cold conditions during the first days of life. In human adults, a significant response to cold was present in patients that had suffered from severe stroke or traumatic brain injury, when submitted to hypothermia.[25] Interestingly, several animal and human studies have reported an elevation in Tb following severe traumatic brain injury or global hypoxia ischemia in the absence of therapeutic hypothermia.[26–28] The brain lesions reported in these animal experiments share

interesting parallels with specific MRI patterns of injury in term neonates after moderate to severe HIE.[29] Furthermore, as in our population, seizures are more common in more severely asphyxiated subjects, and are associated with an increase in neuronal activity and brain metabolic rate (BMR). [30] Indirect effects of a severe hypoxic ischemic insult could also have caused the faster drop in Tb of the +PB infants by an increased heat loss secondary to either hyperventilation or vasodilatation (secondary to hypoxia). Barbiturates administration can also cause vasodilatation.[31] However, in our study, apart from the use of barbiturates, there were no differences in inotropes and other anti-convulsants between +PB and −PB infants. Therefore, differences in the thermogenic response of moderate and severely asphyxiated infants submitted to hypothermia with or without PB require further investigation.

Esophageal temperature before initiation of cooling

In this study we found that +PB infants had significantly lower Te before the initiation of cooling which may have been related to a direct effect of the barbiturate administration. Indeed, the inhibition of the brain metabolic activity is the primary explanation for the hypothermia often seen in patients who undergo general anesthesia with barbiturates. [32,33] In neonates, BMR is a major contributor to overall metabolic rate [34] and PB used as an anti-convulsant medication decreases BMR within 10–15 minutes of its administration when given at doses between 10–15mg/kg.[35,36] Therefore, we speculate that administration of PB has affected BMR and thermogenesis, decreasing baseline values of Tb which in turn were associated with an earlier time to reach Tb during the induction phase of hypothermia. In this particular analysis the number of infants treated with other anti-convulsants such as diazepam or phenytoin is too small for any comparisons between these drugs and PB.

This study was not designed and did not have the objective to evaluate the use of PB alone or in combination with hypothermia as a neuroprotective therapy for infants with HIE. Due to the small sample size we did not investigate any differences in short- and long-term outcomes between +PB and −PB infants. Also, it is possible that the administration of PB at any point during hypothermia would affect thermogenesis and temperature control of these infants. This was not investigate since it would require data on the exact time of PB administration and close monitoring of Te and blanket temperature during the following hours.

In summary, +PB infants were more severely asphyxiated based on neurological exam and presence of clinical seizures, had lower Te at the initiation of cooling and a different trajectory of Te during the induction phase hypothermia. These differences in Te trajectory between the groups may reflect a decreased thermogenic capacity secondary to the use of barbiturates or a more severe brain injury. Further studies are needed to understand the effects of active cooling on thermogenesis in HIE infants with or without PB and potentially help optimize cooling regimens in future studies.

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References

1. Gluckman PD, Wyatt JS, Azzopardi D, et al. Selective head cooling with mild systemic hypothermia after neonatal encephalopathy: multicentre randomised trial. Lancet. 2005; 365(9460): 663–670. [PubMed: 15721471]
2. Shankaran S, Laptook AR, Ehrenkranz RA, et al. Whole-body hypothermia for neonates with hypoxic-ischemic encephalopathy. N Engl J Med. 2005; 353(15):1574–1584. [PubMed: 16221780]
3. Azzopardi DV, Strohm B, Edwards AD, et al. Moderate hypothermia to treat perinatal asphyxial encephalopathy. N Engl J Med. 2009; 361(14):1349–1358. [PubMed: 19797281]
4. Zhou WH, Cheng GQ, Shao XM, et al. Selective head cooling with mild systemic hypothermia after neonatal hypoxic-ischemic encephalopathy: a multicenter randomized controlled trial in china. J Pediatr. 2010; 157(3):367–372. 372. [PubMed: 20488453]
5. Simbruner G, Mittal RA, Rohlmann F, Muche R. Systemic Hypothermia After Neonatal Encephalopathy: Outcomes of neo. nEURO. network RCT. Pediatrics. 2010

6. Jacobs SE, Morley CJ, Inder TE, et al. Whole-Body Hypothermia for Term and Near-Term Newborns With Hypoxic-Ischemic Encephalopathy: A Randomized Controlled Trial. Arch Pediatr Adolesc Med. Apr 4.2011
7. Hey EN. The relation between environmental temperature and oxygen consumption in the new-born baby. J Physiol. 1969; 200(3):589–603. [PubMed: 5765849]
8. Frappell PB, Leon-Velarde F, Aguero L, Mortola JP. Response to cooling temperature in infants born at an altitude of 4,330 meters. Am J Respir Crit Care Med. 1998; 158(6):1751–1756. [PubMed: 9847263]
9. Sahni, R.; Schulze, K. Neonatal thermal regulation. In: Polin, R.; Fox, W., editors. Fetal and Neonatal Physiology. 3. Philadelphia: W.B. Saunders; 2004. p. 676-702.
10. Burnard ED, Cross KW. Rectal temperature in the newborn after birth asphyxia. Br Med J. 1958; 2(5106):1197–1199. [PubMed: 13584896]
11. Painter MJ, Scher MS, Stein AD, et al. Phenobarbital compared with phenytoin for the treatment of neonatal seizures. N Engl J Med. 1999; 341(7):485–489. [PubMed: 10441604]
12. Glass HC, Wirrell E. Controversies in neonatal seizure management. J Child Neurol. 2009; 24(5): 591–599. [PubMed: 19218527]
13. Buchthal F, Svensmark O, Simonsen H. Relation of eeg and seizures to phenobarbital in serum. Arch Neurol. 1968; 19(6):567–572. [PubMed: 4973214]
14. Kokwaro GO, Ogutu BR, Muchohi SN, Otieno GO, Newton CR. Pharmacokinetics and clinical effect of phenobarbital in children with severe falciparum malaria and convulsions. Br J Clin Pharmacol. 2003; 56(4):453–457. [PubMed: 12968992]
15. Belopavlovic M, Buchthal A. Barbiturate therapy in the management of cerebral ischaemia. Anaesthesia. 1980; 35(3):271–278. [PubMed: 7396138]
16. Shankaran S, Laptook AR, McDonald SA, et al. Temperature profile and outcomes of neonates undergoing whole body hypothermia for neonatal hypoxic-ischemic encephalopathy. Pediatr Crit Care Med. Apr 14.2011
17. Gordon CJ, McMahon B, Richelson E, Padnos B, Katz L. Neurotensin analog NT77 induces regulated hypothermia in the rat. Life Sci. 2003; 73(20):2611–2623. [PubMed: 12967685]
18. Gordon CJ. The therapeutic potential of regulated hypothermia. Emerg Med J. 2001; 18(2):81–89. [PubMed: 11300205]
19. Katz LM, Young AS, Frank JE, Wang Y, Park K. Regulated hypothermia reduces brain oxidative stress after hypoxic-ischemia. Brain Res. 2004; 1017(1–2):85–91. [PubMed: 15261103]
20. Mortola JP, Dotta A. Effects of hypoxia and ambient temperature on gaseous metabolism of newborn rats. Am J Physiol. 1992; 263(2 Pt 2):R267–R272. [PubMed: 1510168]
21. Mortola JP. How newborn mammals cope with hypoxia. Respir Physiol. 1999; 116(2–3):95–103. [PubMed: 10487295]
22. Mortola JP, Naso L. Thermogenesis in newborn rats after prenatal or postnatal hypoxia. J Appl Physiol. 1998; 85(1):84–90. [PubMed: 9655759]
23. Herpin P, Wosiak F, Le DJ, Bertin R. Effects of acute asphyxia at birth on subsequent heat production capacity in newborn pigs. Res Vet Sci. 1999; 66(1):45–49. [PubMed: 10088711]
24. Osaka T. Thermogenesis elicited by skin cooling in anaesthetized rats: lack of contribution of the cerebral cortex. J Physiol. 2004; 555(Pt 2):503–513. [PubMed: 14578483]
25. Polderman KH, Herold I. Therapeutic hypothermia and controlled normothermia in the intensive care unit: practical considerations, side effects, and cooling methods. Crit Care Med. 2009; 37(3): 1101–1120. [PubMed: 19237924]
26. Thompson HJ, Tkacs NC, Saatman KE, Raghupathi R, McIntosh TK. Hyperthermia following traumatic brain injury: a critical evaluation. Neurobiology of Disease. 2003; 12(3):163–173. [PubMed: 12742737]
27. Polderman KH. Induced hypothermia and fever control for prevention and treatment of neurological injuries. Lancet. 2008; 371(9628):1955–1969. [PubMed: 18539227]
28. Laptook A, Tyson J, Shankaran S, et al. Elevated temperature after hypoxic-ischemic encephalopathy: risk factor for adverse outcomes. Pediatrics. 2008; 122(3):491–499. [PubMed: 18762517]

29. Miller SP, Ramaswamy V, Michelson D, et al. Patterns of brain injury in term neonatal encephalopathy. J Pediatr. 2005; 146(4):453–460. [PubMed: 15812446]

30. Grant PE, Roche-Labarbe N, Surova A, et al. Increased cerebral blood volume and oxygen consumption in neonatal brain injury. J Cereb Blood Flow Metab. 2009; 29(10):1704–1713. [PubMed: 19675563]

31. Charney, DS.; Mihic, SJ.; Harris, RA. The pharmacological basis of therapeutics. 11. New York: McGraw-Hill; 2006. Hypnotics and sedatives; p. 401-427.

32. Kiyatkin EA, Brown PL. Brain and body temperature homeostasis during sodium pentobarbital anesthesia with and without body warming in rats. Physiol Behav. 2005; 84(4):563–570. [PubMed: 15811391]

33. Erickson KM, Lanier WL. Anesthetic technique influences brain temperature, independently of core temperature, during craniotomy in cats. Anesth Analg. 2003; 96(5):1460–1466. table. [PubMed: 12707150]

34. Sahni, R.; Schulze, K. Temperature control in the newborn infants. In: Polin, R.; Fox, W.; Abman, S., editors. Fetal and Neonatal Physiology. 3. Philadelphia: Saunders; 2004. p. 548-569.

35. Michenfelder JD. Hypothermia plus barbiturates: apples plus oranges? Anesthesiology. 1978; 49(3):157–158. [PubMed: 686435]

36. Steen PA, Michenfelder JD. Mechanisms of barbiturate protection. Anesthesiology. 1980; 53(3): 183–185. [PubMed: 7425330]

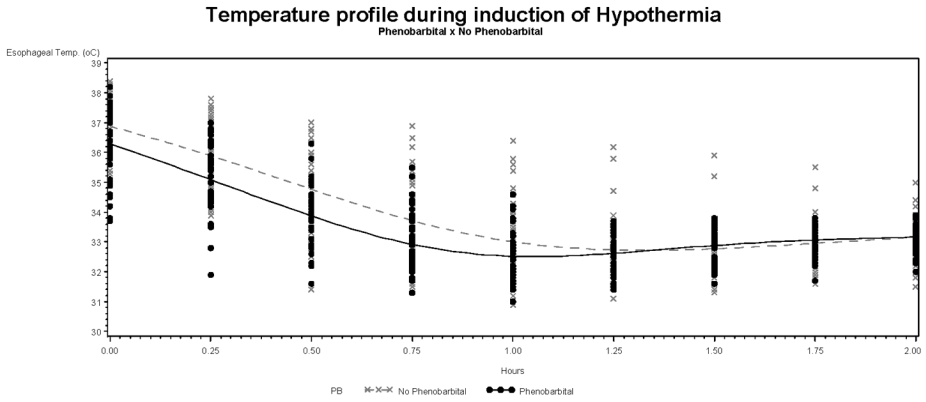

Figure 1.
Esophageal temperature profile in +PB and −PB infants during the induction phase of hypothermia.

Table 1

Baseline characteristics

	No Phenobarbital (n = 54)	Phenobarbital (n = 44)	*p* value
Outborn	19 (35)	28 (64)	<0.01
Cord pH	6.91 ± 0.18	6.80 ± 0.19	<0.02
Apgar 10 min (median, quartiles)	4 (3–5)	4 (1–5)	0.35 *
Cord Base deficit (mEq/L)	17.4 ± 6.5	19.9 ± 6.9	0.07
Birth weight (g)	3416 ± 618	3358 ± 620	0.75
Gestational age (wk)	39.1 ± 1.7	39.0 ± 1.5	0.81
Age of randomization (hrs)	4.1 ± 1.3	4.5 ± 1.2	0.10
Seizures	8 (15)	35 (80)	< 0.0001
Moderate HIE #	43 (80)	23 (53)	0.008
Severe HIE #	11 (20)	20 (47)	
Use of medications prior to initiation of therapeutic hypothermia			
Analgesics	6 (11)	6 (14)	0.76
Other anti-convulsants	5 (9)	10 (23)	0.09
Neuromuscular blocking agents	3 (6)	1 (2)	0.63
Vasopressor	16 (30)	17 (39)	0.39

* Median Two-Sample Test. All other p-values are Fisher's Exact Test (categorical) or Wilcoxon Two-Sample Test (means).

One +PB infant did not have the neurological exam but was included in the hypothermia study due to seizures.

Table 2

Effects of Phenobarbital administration prior to initiation of therapeutic hypothermia on the profile of the esophageal temperature (Te) during the induction phase.

	No Phenobarbital (N=54)					Phenobarbital (N=44)				
	Mean	**SD**	**Q1**	**Median**	**Q3**	**Mean**	**SD**	**Q1**	**Median**	**Q3**
Time to surpass 33.5°C (hours) †	0.99	0.51	0.75	1.00	1.25	0.77	0.39	0.50	0.75	0.75
Time to reach the minimum Te below 33.5°C (hours) †	1.43	0.93	1.00	1.25	1.50	1.24	1.15	0.75	1.00	1.25
Minimum temperature below the target (°C)	32.2	0.5	31.8	32.2	32.5	32.1	0.7	31.7	32.1	32.4
Depth of minimum Te below 33.5°C (°C)	1.3	0.5	1.00	1.3	1.7	1.4	0.7	1.1	1.4	1.8
Time to stabilize Te at 33.5°C after overshoot (hours)	1.53	3.12	0.50	1.00	1.25	2.34	4.25	0.75	1.00	1.75
Duration of induction, from initiation of cooling (hours)	2.96	3.80	2.00	2.25	2.75	3.60	4.78	1.75	2.00	2.75

† $p \leq 0.01$ (Wilcoxon two-sample test, t approximation).