Supplementary Online Content

Shankaran S, Laptook AR, Pappas A, et al; Eunice Kennedy Shriver National Institute of Child Health and Human Development Neonatal Research Network. Effect of depth and duration of cooling on death or disability at age 18 months among neonates with hypoxic-ischemic encephalopathy: a randomized clinical trial. *JAMA*. doi:10.1001/jama.2017.7218

This supplementary material has been provided by the authors to give readers additional information about their work.

eAppendix. Material for Bayesian Analysis of Optimizing Cooling Trial

Bayesian model and implementation

A log binomial model with level of encephalopathy and main effects of cooling duration and depth and their interaction was used to estimate posterior median of the RRs and 95% credible intervals (CrI). The model also included a random center effect and used neutral priors for treatment effects centered at RR of 1 (95% prior interval, 0.5-2.0).[21] Weakly informative priors were used for all other parameters to exclude large treatment effects and produce conservative estimates of treatment effects.

The log binomial model used is similar to the one we previously described for an interim analysis of the same trial [1]. Let y_{ij} indicate the primary outcome of death or moderate or severe disability for infant *i* in center *j*. We assume y follows a Bernoulli distribution with probability p_{ij} of observing the primary outcome. The full model is specified as:

$$\log(p_{ij}) = \beta_0 + \beta_1 \text{ depth}_i + \beta_2 \text{ duration}_i + \beta_3 \text{ depth}_i \times \text{ duration}_i + \beta_4 \text{ level of HIE}_i + u_j$$

$$u_j \sim \text{Normal}(0, \tau^2),$$

where u_j is the random center effect to account for within center correlation. The binary variables depth and duration are coded as 1 for 32.0°C and 120 hours (experimental interventions) and 0 otherwise; level of HIE is a stratifying variable coded as 1 for severe (0 for moderate).

We used Normal(0,1) priors for β_0 and β_4. This prior is mildly informative since it excludes relative risk effects > 7 (< 0.14). For β_1 and β_2, we used neutral priors in the log RR scale of Normal(0, 0.35^2), which have a 95% prior interval of 0.5–2.0 in the RR scale. For the interaction term β_3, we used a Normal(0, 0.14^2) prior which a priori gives a very small probability of 0.025 of a qualitative interaction (meaning that the effect of longer cooling on the outcome changes direction in the presence or absence of deeper cooling) [2]. A weakly informative half-Normal(0,1) prior was used for τ. We constrained all $p_{ij} < 1$ in the model.

The model was implemented via Markov Chain Monte Carlo (MCMC) methods in JAGS. We used 4 MCMC chains with 20,000 iterations each after an initial burn-in of 20,000 iterations. Trace plots of all parameters were monitored for convergence. We additionally calculated the convergence diagnostic of Gelman-Rubin for all parameters. All point estimates reported are posterior medians.

References

1. Pedroza C, Tyson JE, Das A, Laptook A, Bell EF, Shankaran S, et al. Advantages of Bayesian monitoring methods in deciding whether and when to stop a clinical trial: an example of a neonatal cooling trial. Trials. 2016;17:335.

2. Simon R. Bayesian subset analysis: application to studying treatment-by-gender interactions. Stat. Med. 2002;21:2909–16.

eTable. Maternal and Neonatal Characteristics by the Four Hypothermia Groups[a]

	72 Hours, 33.5°C,n (%) (n=92)	72 Hours, 32.0°C,n(%) (n=84)	120 Hours, 33.5°C,n(%) (n=93)	120 Hours, 32.0°C,n(%) (n=78)
Maternal				
Race[b]				
Black	27 (29%)	24 (29%)	31 (34%)	25 (32%)
White	59 (64%)	54 (65%)	53 (58%)	45 (58%)
Other[b]	6 (7%)	5 (6%)	7 (8%)	7 (9%)
Maternal age, mean (SD), y	27.7 (6.0)	28.6 (7.2)	29.0 (7.0)	27.1 (6.8)
Married	48 (53%)	45 (54%)	52 (57%)	37 (47%)
Gravida, median (IQR)	2 (1-3)	2 (1-3)	2 (1-3)	2 (1-3)
Parity, median (IQR)	1 (1-3)	1 (1-2)	1 (1-3)	1 (1-2)
Pregnancy complications				
Chronic hypertension	16 (17%)	21 (25%)	17 (18%)	16 (21%)
Antepartum hemorrhage	12 (13%)	10 (12%)	8 (9%)	8 (10%)
Thyroid dysfunction	4 (4%)	7 (8%)	2 (2%)	1 (1%)
Diabetes	9 (10%)	12 (14%)	13 (14%)	11 (14%)
Intrapartum complications				
Decelerations in fetal heart rate	71 (78%)	63 (75%)	73 (79%)	61 (79%)
Cord prolapse, rupture or compression	15 (16%)	11 (13%)	13 (14%)	7 (9%)
Uterine rupture	3 (3%)	8 (10%)	6 (6%)	5 (6%)
Maternal pyrexia (≥ 37.6°C)	9 (10%)	14 (17%)	8 (9%)	10 (13%)
Shoulder dystocia	6 (7%)	8 (10%)	8 (9%)	6 (8%)
Maternal hemorrhage	12 (13%)	13 (15%)	17 (18%)	11 (14%)
Rupture of membranes (spontaneous or induced)				
None	28 (31%)	16 (20%)	27 (30%)	22 (31%)
≤ 18 h	54 (61%)	57 (70%)	54 (59%)	40 (56%)
> 18 h	7 (8%)	9 (11%)	10 (11%)	10 (14%)
Rupture of membranes, h				
Mean (SD)	9.3 (7.8)	12.6 (25.5)	12.4 (21.5)	8.9 (8.1)
Median (IQR)	7.5 (2.8-14.1)	7.6 (1.2-15.3)	4.8 (2.1-13.4)	7.0 (2.2-14.3)
Emergency cesarean delivery	58 (63%)	53 (63%)	55 (59%)	52 (67%)
Neonatal				
Age at randomization, h	5.1 (1.0)	4.8 (1.2)	4.8 (1.1)	5.0 (1.7)
Transferred from birth hospital	57 (62%)	57 (68%)	64 (69%)	47 (60%)

eTable. Maternal and Neonatal Characteristics by the Four Hypothermia Groups (continued)[a]

Cooling initiated prior to randomization	70 (74%)	62 (69%)	61 (64%)	59 (71%)
Time to initiation of cooling, mean (SD),h	3.75 (1.28)	4.02 (1.27)	4.06 (1.45)	3.86 (1.38)
Male	51 (55%)	51 (61%)	48 (52%)	52 (67%)
Apgar score ≤ 5				
5 min after birth	77 (84%)	70 (84%)	80 (87%)	63 (82%)
10 min after birth	53 (71%)	49 (62%)	58 (70%)	51 (73%)
Birth weight, g	3225 (532)	3383 (519)	3368 (675)	3501 (613)
Length, cm	50.5 (2.8)	50.7 (3.0)	50.5 (3.0)	51.1 (3.2)
Head circumference, cm	34.0 (1.5)	33.9 (2.2)	34.0 (1.7)	34.5 (1.8)
Intubation in delivery room	70 (76%)	65 (77%)	76 (82%)	60 (78%)
Continued resuscitation at 10 min	80 (87%)	69 (82%)	83 (90%)	69 (90%)
Time to spontaneous respiration > 10 min	41 (47%)	29 (37%)	40 (47%)	36 (48%)
Cord blood				
pH	6.9 (0.2)	6.9 (0.2)	6.9 (0.2)	7.0 (0.2)
Base deficit	15.8 (8.2)	16.3 (7.4)	16.3 (6.9)	15.5 (6.3)
Seizures[c]	26 (28%)	20 (24%)	31 (33%)	25 (32%)
Moderate encephalopathy	71 (77%)	64 (76%)	75 (81%)	53 (68%)
Severe encephalopathy	21 (23%)	20 (24%)	18 (19%)	25 (32%)
Inotropic support[c]	23 (25%)	19 (23%)	12 (13%)	21 (27%)
Anticonvulsants[c]	15 (18%)	14 (19%)	15 (19%)	10 (15%)

Abbreviation: IQR interquartile range

[a] Percentages are based on the number of mothers or infants for whom data were available. Because of rounding, not all percentages sum to 100.

[b] Other race includes American Indian or Alaskan Native, Asian, Native Hawaiian or other Pacific Islander, and more than one race.

[c] Data are for this characteristic at the time of randomization.

Encephalopathy was defined as the presence of either moderate or severe signs in at least 3 of the following 6 categories: 1) level of consciousness (moderate is lethargic, severe is stupor or coma), 2) spontaneous activity (moderate is decreased activity, severe is no activity), 3) posture (moderate is distal flexion or complete extension, severe is decerebrate), 4) tone (moderate is hypotonia, severe is flaccid), 5) primitive reflexes (moderate is a weak suck, severe is an absent suck, or moderate is incomplete Moro reflex and severe is absent) and 6) autonomic nervous system; either pupils (moderate is constricted, severe is deviated, dilated or nonreactive to light), heart rate (moderate is bradycardia, severe is variable heart rate) or respiration (moderate is periodic breathing, severe is apnea). The number of moderate or severe signs determined the extent of the encephalopathy; if signs were equally distributed, the designation was based on the level of consciousness.

eFigure.