Selective Head Cooling with Mild Systemic Hypothermia after Neonatal Hypoxic-Ischemic Encephalopathy: A Multicenter Randomized Controlled Trial in China

Wen-hao Zhou, MD, Guo-qiang Cheng, MD, Xiao-mei Shao, Prof, Xian-zhi Liu, MD, Ruo-bing Shan, Prof, De-yi Zhuang, MD, Cong-le Zhou, MD, Li-zhong Du, Prof, Yun Cao, MD, Qun Yang, MD, and Lai-shuan Wang, MD, for the China Study Group*

Objective To investigate the efficacy and safety of selective head cooling with mild systemic hypothermia in hypoxic-ischemic encephalopathy (HIE) in newborn infants.

Study design Infants with HIE were randomly assigned to the selective head cooling or control group. Selective head cooling was initiated within 6 hours after birth to a nasopharyngeal temperature of 34° ± 0.2°C and rectal temperature of 34.5° to 35.0°C for 72 hours. Rectal temperature was maintained at 36.0° to 37.5°C in the control group. Neurodevelopmental outcome was assessed at 18 months of age. The primary outcome was a combined end point of death and severe disability.

Results One hundred ninety-four infants were available for analysis (100 and 94 infants in the selective head cooling and control group, respectively). For the selective head cooling and control groups, respectively, the combined outcome of death and severe disability was 31% and 49% (OR: 0.47; 95% CI: 0.26-0.84; *P* = .01), the mortality rate was 20% and 29% (OR:0.62; 95% CI: 0.32-1.20; *P* = .16), and the severe disability rate was 14% (11/80) and 28% (19/67) (OR: 0.40; 95% CI: 0.17-0.92; *P* = .01).

Conclusions Selective head cooling combined with mild systemic hypothermia for 72 hours may significantly decrease the combined outcome of severe disability and death, as well as severe disability. *(J Pediatr 2010;157:367-72)*.

See editorial, p 351 and related articles, p 361 and p 499

Hypoxic-ischemic encephalopathy (HIE) remains a major cause of neonatal death and long-term disabilities.[1,2] Although there has been tremendous progress in neonatal care, management strategies that minimize the morbidity of HIE have been limited. Data from animal studies showed protective effects of mild hypothermia to immature brain,[3,4] and the critical timing for mild hypothermia was within 6 hours after hypoxic-ischemic injury and for a period of 24 to 72 hours.[3,5-8] Gunn et al[9] reported a pilot study of mild hypothermia for HIE in 1998. Since then, several studies have shown a trend for brain protection with mild to moderate hypothermia.[10-15] Three multicenter randomized controlled trials (RCTs) were published currently,[16-18] and another 3 RCTs are being completed or have been completed including ICE Trial (Australian), neo.nEuro.network Trial (European)[19, 20] and this study.

Since 1998, research about the neuroprotective effect of mild hypothermia for HIE has been performed in China.[21-26] We reported a pilot study to investigate the efficacy and safety of selective head cooling in HIE newborn infants in 2002 that showed that selective head cooling was safe, simple, useful, and effective.[27] Reassured by our results, we organized a multicenter RCT of selective head cooling combined with mild systemic hypothermia to treat in infants with HIE.

Methods

This study involved the participation of 12 children's hospitals or children's and women's health care centers. The protocol was designed by the neonatologists at Children's Hospital of Fudan University and a consensus was reached by the participating hospitals. Written informed consent was obtained from parents before enrollment. This study was approved by the ethics committee of the Children's Hospital of Fudan University.

Infants were screened for eligibility if they had a gestational age ≥ 37 weeks and birth weight ≥2500 g and were admitted to the neonatal intensive care

HIE	Hypoxic-ischemic encephalopathy
RCT	Randomized controlled trial

From the Children's Hospital of Fudan University, Shanghai (W.Z., G.C., X.S., Y.C., Q.Y., L.W.), Guangxi Maternity and Infant Health Hospital, Guangxi Province (X.L.), Qingdao Children's Hospital, Shandong Province (R.S.), Quanzhou Children's Hospital, Fujian Province (D.Z.), The First Hospital of Beijing University, Beijing (C.Z.), and Children's Hospital of Zhejiang University, Zhejiang Province (L.D.), China

*A list of members of The China Study Group is available at www.jpeds.com (Appendix).

Supported by grants from Construction of Key Disciplines of 211 Engineering of Ministry of Education of People's Republic of China. The authors declare no conflicts of interest.

Registration number at Clinicaltrials.gov: NCT00890409.

 10.1016/j.jpeds.2010.03.030

unit within 6 hours of age with clinical evidence of exposure to perinatal hypoxia-ischemia or a diagnosis of encephalopathy. Inclusion criteria were as follow: an Apgar score ≤3 at 1 minute and ≤5 at 5 minutes; cord blood gas pH <7.0 or base deficit ≤16 mmol/L; and need for resuscitation or ventilation at 5 minutes of age. Eligible infants then underwent a standardized neurologic examination performed by a certified examiner. The severity of HIE (mild, moderate and severe) was assessed according to criteria of Sarnat and Sarnat,[28] including lethargy, stupor, or coma, with 1 or more of the findings of hypotonia, abnormal reflexes, or clinical seizure.

Exclusion criteria were as follow: (1) Major congenital abnormalities; (2) Infection (rupture of membranes >18 hours or maternal fever >38°C or amniotic fluid foul smell); (3) Other encephalopathy (neonatal stroke, central nervous system abnormality, intracranial hemorrhage diagnosed by CT or head ultrasonography); (4) Severe anemia (hemoglobin <120 g/L).

The randomization codes were generated by computer and supplied in numbered, sealed opaque envelopes. After informed consent was obtained from a parent, the assignment to a treatment or control group was performed by telephone. Assignments were stratified according to center in a randomized block design with a block size of 6.

The Procedure for Selective Head Cooling and Temperature Monitoring

A semiconductor controlled water circulation cooling device (YJW608-04B; Henyang Radio Manufactory, Hunan, China) was used for head cooling. Infants were fitted with a cooling cap around the head. The temperature of the cap could be regulated by a servocontrolled temperature probe placed in the nasopharynx to maintain the nasopharyngeal temperature at (34° ± 0.2°C). Infants were nursed under a radiant warmer, which was servocontrolled to the infant's abdominal skin temperature and adjusted to maintained rectal temperature at 34.5° to 35°C. Head cooling was started within 6 hours of age and continued for 72 hours, followed by spontaneous rewarming. Infants in the control group were cared for on radiant warmers, which were servocontrolled to the infant's abdominal skin temperature to maintained rectal temperature at 36° to 37.5°C. Infants in both groups received the same clinical care and monitoring of vital signs and surveillance for organ dysfunction aside from selective head cooling or normothermia.

Ventilation, inotropes, anticonvulsant medications, and mannitol (if infants had bulging fontanelle or status epilepticus) were used as required. Both groups received total parenteral nutrition, and oral feeding was started by 3 days of age.

Monitoring

Nasopharyngeal and rectal temperature, oxygen saturation, respiratory rate, heart rate and blood pressure were monitored with the Siemens-SC6000 monitor (Siemens, Berlin, Germany) in both groups. We measured blood gases, electrolytes, blood glucose, liver function tests, renal function tests, and complete blood count according to a standardized protocol(before treatment, 12 hours, 24 hours, 48 hours,72 hours after treatment). Blood gas measurements were corrected for body temperature. Electrocardiography was performed if bradycardia of less than 80 beats/min or arrhythmia was suspected.

Adverse Events

We defined major adverse events as severe arrhythmia (II or III degree A-V block or atrial or ventricular arrhythmia), major venous thrombosis (ie, thrombosis of a major vessel not related to an infusion line), refractory hypotension (mean blood pressure less than 40 mm Hg despite full support), moderate or severe scleredema (greater or equal to 20% body surface area),[29] and severe bleeding (disseminated intravascular coagulation, lung hemorrhage, gastrointestinal hemorrhage and gross hematuria).

We defined common adverse events as mild arrhythmia (sinus bradycardia if heart rate <80 beats/min, prolonged QT interval, occasional premature beats, and I degree A-V block), mild scleredema (less than 20% body surface area), renal dysfunction (creatinine >120 μmol/L, blood urea nitrogen >8 mmol/L or urine output <1 mL/kg/h), liver dysfunction (alanine transaminase >100 U/L), thrombocytopenia (platelet $<100 \times 10^9$/L), serum electrolytes or biochemical abnormalities (sodium <130 mmol/L or >150 mmol/L, potassium <3.5 mmol/L or >5.5 mmol/L, calcium <2.0 mmol/L, blood glucose >8 mmol/L or <2.6 mmol/L).

Follow-Up

The primary outcome was the combined endpoint of death and severe disability at 18 months of age. Survivors returned for follow-up had a neurologic examination by certified staff blinded to the treatment group, and a neurodevelopmental assessment with the Gesell Child Development Age Scale[30] and the Gross Motor Function Classification System (GMFCS).[31] GMFCS level 3-5 or DQ <70 were defined as severe disability. For infants who did not return for follow-up, we obtained information on neurodevelopment outcomes assessed by the trained pediatrician in local child health care or rehabilitation department.

Statistical Analysis

The baseline mortality or severe disability rate in the control group was estimated at 50%. To detect an absolute decrease of 20% to 30% in the selective head cooling group, with a 2-sided test with an alpha of 0.05 and power of 80%, and an estimated 20% loss to follow-up, 228 (114 in each group) patients were needed.

All data analyses were performed according to the intention-to-treat principle. Mean ± SD was used for normally distributed data. Between-group comparisons of continuous variables were conducted with the Student *t* test. Proportions are presented as percentages, and between-group comparisons were conducted with χ^2 test or Fisher exact test. Multinomial logistic regression was done incorporating the sex, seizure, and fever variables. An external data and safety monitoring committee monitored safety and efficacy during analyses. SPSS 13.0 (SPSS, Inc., Chicago, Illinois) was used for statistical analysis. Alpha set at 0.05, and all tests were 2-tailed.

Results

From May 2003 to August 2005, a total of 256 cases were recruited. Figure 1 (available at www.jpeds.com) shows the trial profile. Twenty-one infants (19 and 2 infants in the selective head cooling and control group) were excluded because the pediatricians in the local hospitals did not follow the scheduled random methods.

Characteristics and Monitoring of Infants

There were no statistically significant differences in baseline characteristics (Table I). The average time of onset of treatment was 4.1 ± 1.2 hours after delivery in the selective head cooling group, of which 61 cases (51.2%) were started within 4 hours. The average time to reach the target nasopharyngeal temperature was about 2 hours, and the nasopharyngeal temperature was maintained about 34°C, and the rectal temperature was maintained between 34.5° and 35.0°C during hypothermia. After 72 hours hypothermia, spontaneous rewarming began, and the average time to reach 36.5°C for rectal temperature was 12.5 ± 6.1 hours. There were no adverse events during the rewarming period. In the control group, the average value of nasopharyngeal and rectal temperature was stable and maintained at about 36°C to 36.5°C. The changes over time of the nasopharyngeal and rectal temperatures are shown in Figure 2, A (available at www.jpeds.com).

Adverse Events

Heart rate decreased on average 20 to 30 beats/min compared with the control group during hypothermia, but there were only 4 cases (4%) with heart rates less than 80 beat/min. The changes over time of heart rate are shown in Figure 2, B (available at www.jpeds.com). Scalp edema occurred in 22 cooled infants and recovered rapidly after the cooling. There were 2 cases of mild edema and scleredema during hypothermia, which recovered after rewarming. Death, major, and other adverse events were similar between the 2 groups (Table II), which means there is no significant adverse events of hypothermia therapy on neonatal HIE.

Primary and Secondary Outcome

Primary outcome were available for 194 infants, including 5 cases in the selective head cooling and 4 cases in the control group were assessed by local hospitals. Among the 5 cases in the selective head cooling group, there were 2 mild and 3 moderate HIE cases without severe disabilities. Among the 4 cases in the control group, there were 1 mild, 2 moderate, and 1 severe HIE cases, and 2 of the cases had development of cerebral palsy.

The combined incidence of death and major disability was lower in the selective head cooling group than that in the control groups (Table III). Among the 11 infants with disability in the selective head cooling group, 7 had cerebral palsy, 3 had cerebral palsy with mental retardation, and 1 had mental retardation. Nineteen cases in the control group had cerebral palsy, and 13 of these also had mental retardation. We repeated the analysis after exclusion of the 9 infants whose outcomes were assessed by telephone communication. The incidence of death or severe disability was significantly decreased in the selective head cooling group (33%) compared with the control group (49%) (OR: 0.51; 95% CI: 0.28-0.92; $P = .024$).

A total of 138 infants (75 and 63 infants in the selective head cooling and control group respectively) had the Gesell Child Development Scale score. The average DQ score was

Table I. Baseline characteristics

	Head cooling (n = 100)	Control (n = 94)	P
Mode of delivery			.89
Cesarean	40 (40%)	36 (38%)	
Assisted*	24 (24%)	21 (22%)	
Spontaneous	36 (36%)	37 (40%)	
Male	87 (87%)	78 (83%)	.43
Complications of pregnancy	50 (50%)	40 (43%)	.3
Fetal distress	73 (73%)	66 (70%)	.67
Seizures	49 (49%)	44 (47%)	.76
Assist ventilation†	16 (16%)	22 (23%)	.2
Transferred from birth hospital	77 (77%)	77 (82%)	.4
Severity of HIE			.92
Mild	21 (21%)	18 (19%)	
Moderate	41 (41%)	41 (44%)	
Severe	38 (38%)	35 (37%)	
5-minute Apgar score ≤5	80 (80%)	71 (76%)	.46
Birth weight (g)	3360 ± 483	3299 ± 421	
Onset of therapy (hours after birth)	4.1 ± 1.2	4.0 ± 1.7	.19

*Include assisted delivery by forceps and vacuum extraction.
†CPAP: selective head cooling 1, control 3.

Table II. Death, major, and other head cooling adverse events

	Head cooling (n = 100)	Control (n = 94)	P
Major adverse events	3 (3%)	3 (3.2%)	1
Major cardiac arrhythmia	0	1 (1.1%)	.49
Severe hemorrhage	3 (3%)	2 (2.1%)	.68
Major venous thrombosis	0	0	
Complication during 96 of treatments			
Raised BUN	23 (23%)	21 (22%)	.91
Raised creatinine	21 (21%)	19 (20%)	.89
Oliguria	7 (7%)	4 (4.3%)	.54
Raised liver enzymes	35 (35%)	26 (28%)	.27
Hypocalcemia	40 (40%)	33 (35%)	.21
Hypokalemia	10 (10%)	16 (17%)	.15
Hyperkalemia	25 (25%)	20 (21%)	.54
Hyponatremia	12 (12%)	14 (14.9)	.55
Hypoglycemia	7 (7%)	2 (2%)	.17
Hyperglycemia	7 (7%)	3 (3%)	.33
Metabolic acidosis	7 (7%)	7 (7.4%)	.9
Platelet count <100 000 per μL	6 (6%)	2 (2%)	.28
Cause of death			.88
HIE	7 (35%)	12 (44%)	
Respiratory failure	3 (20%)	5 (19%)	
Kidney failure	2 (10%)	3 (11%)	
Severe hemorrhage	3 (15%)	2 (7%)	
Others	5 (25%)	5 (19%)	
Distribution of age at death			.13
≤3 days	8 (40%)	17 (63%)	
4-7 days	4 (20%)	6 (22%)	
>7 days	8 (40%)	4 (14%)	

BUN, Blood urea nitrogen.

Table III. Primary and secondary outcomes and components

	Head Cooling	Control	OR (95%CI)	*P*
Primary outcomes				
Death or severe disability	31/100 (31%)	46/94 (49%)	0.47 (0.26-0.84)	.01
Death	20/100 (20%)	27/94 (29%)	0.62 (0.32-1.20)	.16
Severe disability	11/80 (14%)	19/67 (28%)	0.40 (0.17-0.92)	.03
Secondary outcomes				
Death or severe disability				
Infants with moderate to severe HIE	31/79 (39%)	46/76 (61%)	0.42 (0.22-0.80)	.01
Infants with moderate HIE	9/41 (22%)	19/41 (46%)	0.33 (0.16-0.85)	.02
Infants with severe HIE	22/38 (58%)	27/35 (77%)	0.41 (0.15-1.13)	.08
Survival with severe disability				
Infants with moderate to severe HIE	11/59 (24%)	19/49 (41%)	0.36 (0.15-0.87)	.02
Infants with moderate HIE	6/38 (24%)	15/37 (39%)	0.49 (0.18-1.33)	.21
Infants with severe HIE	5/21 (24%)	4/12 (33%)	0.63 (0.13-2.99)	.18
DQ of total infants*				
Median (range)	93 (45-112)	89 (22-115)		.045
DQ<70 (%)	4/75 (5%)	13/63 (21%)	0.22 (0.07-0.70)	.01
DQ 70-84 (%)	23/75 (31%)	17/63 (27%)	1.2 (0.57-2.51)	.64
DQ≥85 (%)	48/75 (64%)	33/63 (52%)	1.61 (0.82-3.20)	.17
DQ of infants with moderate to severe HIE				
Median (range)	91 (45-112)	81 (22-107)		.04
DQ<70 (%)	4/56 (7%)	13/48 (27%)	0.21 (0.06-0.69)	.01
DQ 70-84 (%)	17/56 (31%)	10/48 (21%)	1.70 (0.69-4.19)	.27
DQ≥85 (%)	35/56 (62%)	25/48 (52%)	1.53 (0.70-3.36)	.32

*5 of 80 survival cases in selective head cooling group (6.2%) and 4 of survival 67 cases (6%) in control group did not have the Gesell development score

significantly higher in the selective head cooling and than that in the control groups, $P = .02$ (Table III).

Correlation Between Death or Severe Disability and Sex, Fever, and Seizure in Infants with Moderate to Severe HIE

Fever was defined as temperature > 38.0°C at least once to an age of 96 hours. Eleven infants (5 and 6 infants in the selective head cooling and control group) had a fever. The hypothermia occurred during the rewarming period in the 5 infants in the selective head cooling group. In the control group, 2, 1, 2, and 1 infant had a fever within the first 24 hours, 24 to 48 hours, 48 to 72 hours, and 72 to 96 hours, respectively. Seizures were diagnosed clinically. Forty-nine infants (33 and 16 infants before treatment and during treatment, respectively) and 44 infants (30 and 14 infants before treatment and during treatment, respectively) had a seizure in the selective head cooling and control groups, respectively. The rate of death and major disability among infants with fever, seizures, and male sex, respectively, was 5/13 (38%), 22/49 (45%), and 27/70 (39%) in the selective head cooling group and 6/14 (43%), 27/44 (61%) and37/62 (60%) in the control group. Multinomial logistic regression showed no correlation between death or severe disability and fever, seizures, and sex ($P = .99$, $P = .37$, $P = .50$, respectively).

Death and Causes of Death

The mortality rate was no significant different between the selective head cooling and control group (Table III). Severe encephalopathy, respiratory failure, kidney failure, and severe hemorrhage were the major causes of death, and most infants died during the first week in both groups (Table II).

Discussion

Hypothermia, whether whole body or selective head cooling, shows great promise on the basis of both animal and human neonatal studies.[3,4,11-15] Three RCT trials demonstrated that hypothermia could improve the combined outcome of death and severe neurodevelopmental disability or an increased rate of survival without neurologic abnormality and reduced risks of cerebral palsy at 18 months of age.[16-18] A recently published meta-analysis[32] also showed the effectiveness of hypothermia for improving the combined outcome of death and neurodevelopment disability after hypoxic ischemic injury. We also found that selective head cooling titrated to a nasopharyngeal temperature of 34°C combined with mild whole-body hypothermia (rectal temperature 34.5° to 35°C) within 6 hours after delivery had a significant brain-protective effect compared with normothermia. The combined outcome of death and severe disability at 18 months for all infants with HIE was significantly decreased in the selective head cooling group compared with the control group.

Hypothermia may be most effective for infants with moderate HIE.[16-18,32] We found a statistically significant benefit of selective head cooling for infants with moderate HIE and a trend for significance among infants with severe HIE.

Fever and clinically defined seizures are important factors that may influence outcome among infants with HIE.[33-36] Multinomial logistic regression demonstrated no effect on fever and seizures outcome in our study. The incidence of seizures was similar in both groups (49% and 47% in the selective head cooling group and in the control group, respectively). These results suggest that hypothermia may not avert the onset of seizures.

We found no significant increase in adverse events such as arrhythmia, major venous thrombosis, moderate to severe scleredema, refractory hypotension, hemorrhage, thrombocytopenia, disseminated intravascular coagulation, or pulmonary hypertension with hypothermia. Indicators of hepatic and renal function and metabolic homeostasis in the selective head cooling group were not different from the control group. There were 2 infants (1.7%) with mild scleredema during hypothermia who recovered after rewarming.

There were several limitations to our study. Despite our best efforts, a significant proportion of our infants were lost to follow-up (16% vs 19% in the selective head cooling and control group, respectively). Second, male infants were the larger proportion in the study. In this study, there was no effect of sex on the outcome in our study.

Our inclusion criteria included all infants with HIE, including those with mild HIE (21% in the selective head cooling group and 19% in control group) and thus included infants who may not have benefited from hypothermia. Our results showed that infants with mild HIE in both groups had no risk of death or major disability, confirming the exclusion of this subgroup in other published studies.[19,20] To make our results more comparable with other published hypothermia studies, we reported the results of subgroup analyses of infants with moderate and severe HIE and found slightly lower rates of adverse outcomes compared with those previously reported. Our inclusion criteria were different from those used in other studies.[16-18] For example, Apgar score <5 at 10 minutes was used as an inclusion criteria[16-18]; in our study, an Apgar score<5 at 5 minutes was used.

Our results add to the evidence that selective head cooling combined with mild systemic hypothermia for 72 hours can decrease death or severe disability among infants with moderate or severe HIE. Hypothermia was well tolerated without major adverse events. Importantly, despite the limited resources for research in China, our study demonstrates the feasibility of conducting a multicentered RCT in China. ■

Acknowledgments available at www.jpeds.com.

Submitted for publication Oct 3, 2009; last revision received Feb 16, 2010; accepted Mar 26, 2010.

Reprint requests: Xiao-mei Shao, 399 Wanyuan Rd, Shanghai, China. E-mail: xiaomeishao.fd@gmail.com.

References

1. Phelan JP, Martin GI, Korst LM. Birth asphyxia and cerebral palsy. Clin Perinatol 2005;32:61-76.
2. Shankaran S, Woldt E, Koepke T, Bedard MP, Nandyal R. Acute neonatal morbidity and long-term central nervous system sequelae of perinatal asphyxia in term infants. Early Hum Dev 1991;25:135-48.
3. Gunn AJ, Gunn TR, de Haan HH, Williams CE, Gluckman PD. Dramatic neuronal rescue with prolonged selective head cooling after ischemia in fetal lambs. J Clin Invest 1997;99:248-56.
4. Tooley JR, Satas S, Porter H, Silver IA, Thoresen M. Head cooling with mild systemic hypothermia in anesthetized piglets is neuroprotective. Ann Neurol 2003;53:65-72.
5. Thoresen M, Penrice J, Lorek A, Cady EB, Wylezinska M, Kirkbride V, et al. Mild hypothermia after severe transient hypoxia-ischemia ameliorates delayed cerebral energy failure in the newborn piglet. Pediatr Res 1995;37:667-70.
6. Ohmura A, Nakajima W, Ishida A, Yasuoka N, Kawamura M, Miura S, et al. Prolonged hypothermia protects neonatal rat brain against hypoxic-ischemia by reducing both apoptosis and necrosis. Brain Dev 2005;27:517-26.
7. Sirimanne ES, Blumberg RM, Bossano D, Gunning M, Edwards AD, Gluckman PD, et al. The effect of prolonged modification of cerebral temperature on outcome after hypoxic-ischemic brain injury in the infant rat. Pediatr Res 1996;39:591-7.
8. Wagner BP, Nedelcu J, Martin E. Delayed postischemic hypothermia improves long-term behavioral outcome after cerebral hypoxia-ischemia in neonatal rats. Pediatr Res 2002;51:354-60.
9. Gunn AJ, Gluckman PD, Gunn TR. Selective head cooling in newborn infants after perinatal asphyxia: a safety study. Pediatrics 1998;102:885-92.
10. Thoresen M, Whitelaw A. Cardiovascular changes during mild therapeutic hypothermia and rewarming in infants with hypoxic-ischemic encephalopathy. Pediatrics 2000;106:92-9.
11. Azzopardi D, Robertson NJ, Cowan FM, Rutherford MA, Rampling M, Edwards AD. Pilot study of treatment with whole body hypothermia for neonatal encephalopathy. Pediatrics 2000;106:684-94.
12. Battin MR, Dezoete JA, Gunn TR, Gluckman PD, Gunn AJ. Neurodevelopmental outcome of infants treated with head cooling and mild hypothermia after perinatal asphyxia. Pediatrics 2001;107:480-4.
13. Shankaran S, Laptook A, Wright LL, Ehrenkranz RA, Donovan EF, Fanaroff AA, et al. Whole-body hypothermia for neonatal encephalopathy: animal observations as a basis for a randomized, controlled pilot study in term infants. Pediatrics 2002;110:377-85.
14. Battin MR, Penrice J, Gunn TR, Gunn AJ. Treatment of term infants with head cooling and mild systemic hypothermia (35.0°C and 34.5°C) after perinatal asphyxia. Pediatrics 2003;111:244-51.
15. Lin ZL, Yu HM, Lin J, Chen SQ, Liang ZQ, Zhang ZY. Mild hypothermia via selective head cooling as neuroprotective therapy in term neonates with perinatal asphyxia: an experience from a single neonatal intensive care unit. J Perinatol 2006;26:180-4.
16. Gluckman PD, Wyatt JS, Azzopardi D, Ballard R, Edwards AD, Ferriero DM, et al. Selective head cooling with mild systemic hypothermia after neonatal encephalopathy: multicentre randomised trial. Lancet 2005;365:663-70.
17. Shankaran S, Laptook AR, Ehrenkranz RA, Tyson JE, McDonald SA, Donovan EF, et al. Whole-body hypothermia for neonates with hypoxic-ischemic encephalopathy. N Engl J Med 2005;353:1574-84.
18. Azzopardi D, Strohm B, Edwards AD, Dyet L, Levene M, Halliday H, et al. Moderate Hypothermia to Treat Perinatal Asphyxial Encephalopathy. N Engl J Med 2009;361:1349-58.
19. Jacobs S, Morley C. Infant Cooling Evaluation Trial. Available at: www.ctc.usyd.edu.au/6registry/PTO367.htm. Accessed November 29, 2005.
20. Simbruner G, neo.nEuro.network. Induced systemic hypothermia in asphyxiated new-born infants: a randomized, controlled, multicenter study. Available at: http://neonatal-research/php/detail.php?artnr_4367&ukatnr_11237&ukatnameDepartment. Accessed November 29, 2005.
21. Mei Qin, Shaozhen Fan. Protective effects of hypothermia in hypoxic-ischemic brain injury in newborn rats (Abstracts). Pediatric Res 1998;44:421.
22. Cheng GQ, Shao XM, Huang HJ. Effects of selective head cooling on cerebral blood flow and cerebral metabolic rate in newborn piglets (in Chinese). Chin J Pediatr 2005;43:748-52.
23. Lijun Yu, Laishuan Wang, Xiaomei Shao. Moderate hypothermia improves the cerebral energy metabolism of hypoxic-ischemic brain damage in the immature rat (English). Chin J Contemp Pediatr 2003;5:192-5.
24. Wang LS, Yu LJ, Shao XM. Mild hypothermia attenuates neuronal apoptosis after cerebral hypoxia-ischemia in neonatal rats (in Chinese). Chin J Contemp Pediatr 2007;9:37-41.

25. Wang LS, Shao XM, Yang Y, Chen L. Effects of moderate hypothermia on p-ERK/p38 MAPK signal pathway following hypoxic-ischemic brain injury in neonatal rats (in Chinese). Chin J Perinat Med 2006;9:337-40.
26. Wang JM, Liu DL, Shao XM. Influence of mild hypothermia treatment on amplitude integrated electroencephalogram in newborn pigs with hypoxic-ischemic brain damage (in Chinese). Chin J Contemp Pediatr 2005;7:159-62.
27. Zhou W, Shao X, Cao Y, Chen C, Zhang X, Fan S, et al. Safety study of hypothermia for the treatment of hypoxic-ischemic brain damage in term neonates. Acta Pharmacol Sin (Suppl) 2002;64-8.
28. Sarnat HB, Sarnat MS. Neonatal encephalopathy following fetal distress: a clinical and electroencephalographic study. Arch Neurol 1976;33:696-705.
29. Wei KL, Ji XC, Wu SM. Guideline of sclerdema neonatorum therapy (in Chinese). Chin J Pediatr 1991;29:163-4.
30. Gesell AL. Gesell and Amatruda's developmental diagnosis: the evaluation and management of normal and abnormal neuropsychologic development in infancy and early. 3rd ed. Hagerstown, ML: Harper & Row; 1974.
31. Palisano R, Rosenbaum P, Walter S, Russel D, Wood E, Galuppi B. Development and reliability of a system to classify gross motor function in children with cerebral palsy. Dev Med Child Neurol 1997;39:214-23.
32. Jacobs S, Hunt R, Tarnow-Mordi W, Inder T, Davis P. Cooling for newborns with hypoxic ischaemic encephalopathy. Cochrane Database Syst Rev 2007;4:CD003311.
33. Naqeeb N, Edwards AD, Cowan FM, Azzopardi D. Assessment of neonatal encephalopathy by amplitude-integrated electroencephalography. Pediatrics 1999;103:1263-71.
34. Wyatt JS, Gluckman PD, Liu PY, Azzopardi D, Ballard R, Edwards AD, et al. Determinants of outcomes after head cooling for neonatal encephalopathy. Pediatrics 2007;119:912-21.
35. Ambalavanan N, Carlo WA, Shankaran S, Bann CM, Emrich SL, Higgins RD, et al. Predicting outcomes of neonates diagnosed with hypoxemic-ischemic encephalopathy. Pediatrics 2006;118:2084-93.
36. Perlman JM. Hyperthermia in the delivery: potential impact on neonatal mortality and morbidity. Clin Perinatol 2006;33:55-63.

50 Years Ago in *THE JOURNAL OF PEDIATRICS*

Sturge-Weber Syndrome; Nonsurgical Management

Smith, AG and Ramsay, AB. J Pediatr 1960;57:585-8

In 1960, the choice of anti-seizure medications was rather limited: phenytoin and phenobarbital were the mainstays of treatment. Ethosuximide was newly available for children with absence ("petit mal") epilepsy. Bromide salts and the ketogenic diet were alternatives. It would be another 14 and 18 years until carbamazepine and valproic acid became available. Phenytoin remains an effective and inexpensive anti-seizure medication; it is the most commonly prescribed anti-seizure medication in the world.

We are fortunate in 2010 to have some 2 dozen medications we can prescribe for epilepsy; however the advantages over older medications have little to do with greater efficacy and everything to do with apparent reduction in the risk of adverse effects and the convenience of simpler dosing regimens.

Fifty years ago in *The Journal*, Smith and Ramsay described the effectiveness of adding phenobarbital (on a 4-times per day dosing regimen) to phenytoin (3-times per day) in a child with uncontrolled seizures caused by Sturge-Weber syndrome. The authors note the then recently described efficacy of hemipsherectomy for intractable epilepsy in children with Sturge-Weber syndrome.[1]

In 2010, with so many once-a-day and twice-a-day anti-seizure medications at our disposal, we sympathize with the parents trying to adhere (in the modern parlance) to the 2 drug/3-times-a-day/4-times-a-day regimen. But a closer reading reveals the authors' advocacy of solid principles we rely on today for treating children with intractable epilepsy: (1) Maximizing the first medication is advisable before adding a second drug; (2) Slow titration is often well tolerated when using a potentially sedating medication like phenobarbital; (3) Control of epilepsy may be transient, and consideration of intervention with epilepsy surgery should be considered when reasonable medications have failed; and (4) Behavior and cognitive symptoms are not entirely attributable to the medications and the underlying epilepsy. Parents' anxiety has a cost, and wise counseling by the pediatrician (and neurologist) to "avoid overprotection and to permit the patient to lead as normal a life as possible" is indispensable.

Donald M. Olson, MD
Departments of Neurology and Pediatrics
Stanford University School of Medicine
Stanford, California
10.1016/j.jpeds.2010.03.026

Reference

1. Krynauw RA. Infantile hemiplegia treated by removing one cerebral hemisphere. J Neurol Neurosurg Psychiatry 1950;13:243-67.

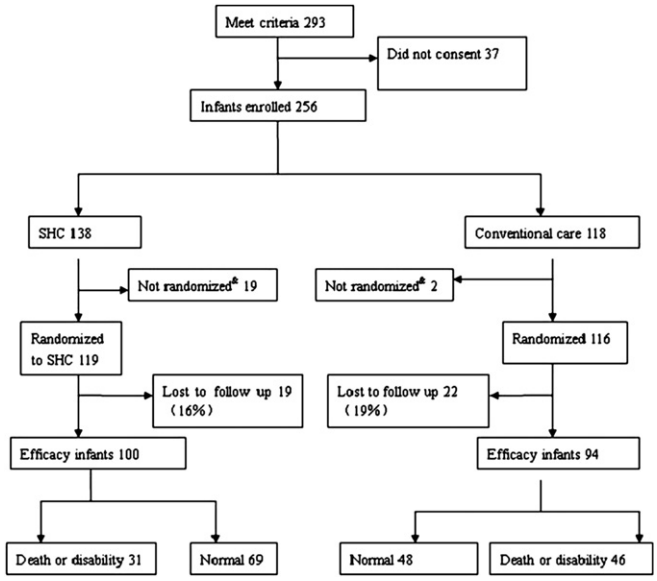

Figure 1. Trial profile.

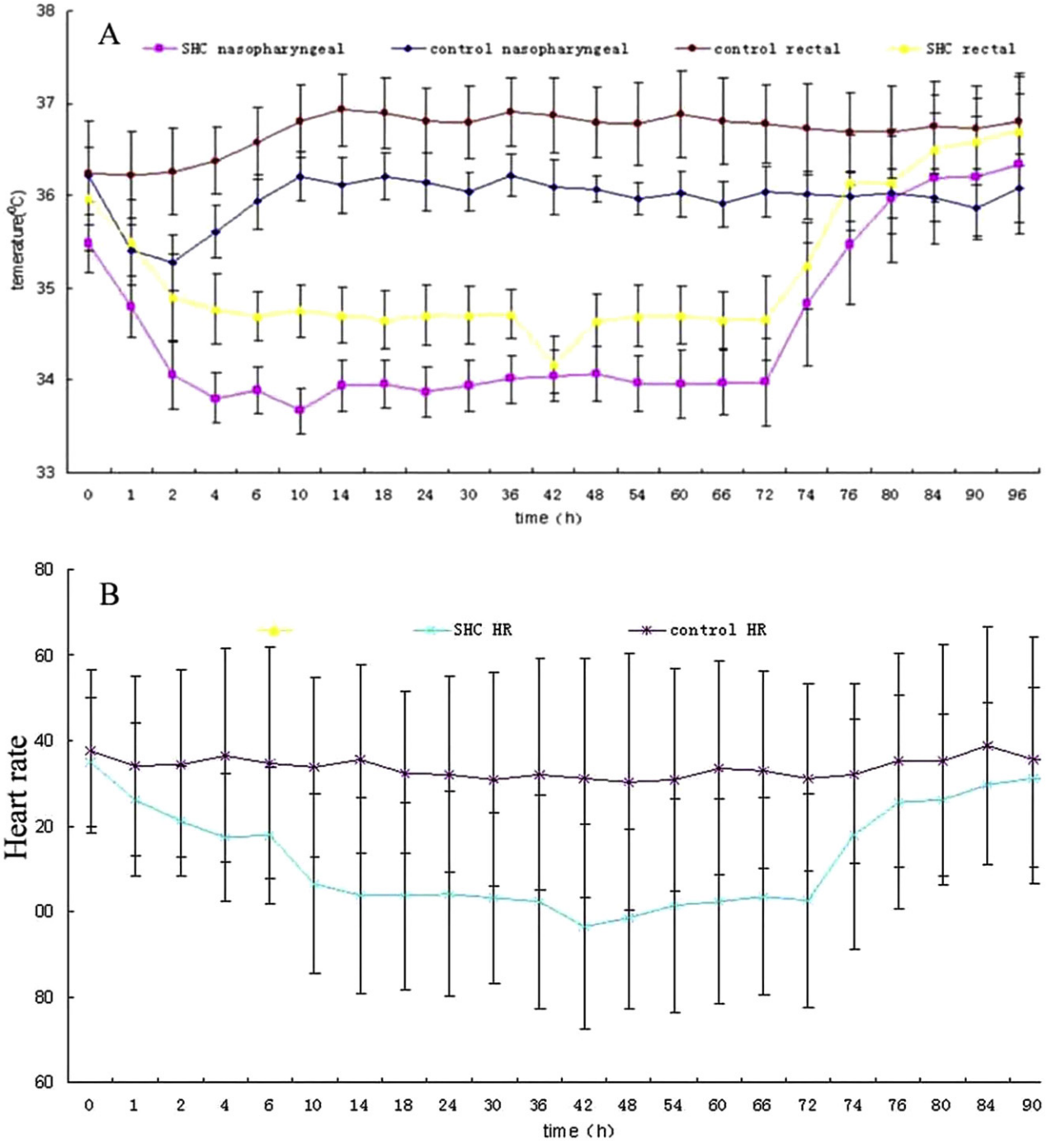

Figure 2. Changes in nasopharyngeal, rectal temperature, and heart rate in selective head cooling and control group.

Appendix

Xiao-mei Shao, Wen-hao Zhou, Guo-qiang Cheng Yun Cao, Lai-shuan Wang, Qun Yang,(Children's Hospital of Fudan University, Shanghai), Xian-zhi Liu (Guangxi Maternity and Infant health Hospital, Guangxi Province); Ruo-bing Shan (Qingdao Children's Hospital, Shandong province); De-yi Zhuang (Quanzhou Children's Hospital Fujian Province); Cong-le Zhou (The First Hospital of Beijing University, Beijing); Li-zhong Du (Children's Hospital of Zhejiang University, Zhejiang province).

Acknowledgements

We are indebted to Kyong-soon Lee from NICU of The Hospital for Sick Children in Toronto for help to review the manuscript, to Jianfeng Luo from Statistics of Fudan University for help with the statistical analysis; to Dr. P. D. Gluckman, A. J. Gunn, and J. Guan for many years' support and guidance; to Dr. S. Shankaran from NICHD Neonatal Research Network for help with the manuscript; to all the neonatal physicians and nurses who involved in the study; to Dr. J. F. Lucey for communication and encourage; and to the families and infants who participated in the study.