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Abstract

Animal studies suggest that hypothermia decreases seizure burden, whereas limited human data are inconclusive. This retrospective cohort study examines the relationship between therapeutic hypothermia and seizure in neonates with hypoxic-ischemic encephalopathy. Our center admitted 224 neonates from July 2004 to December 2011 who met institutional cooling criteria. Seventy-three neonates were born during the pre-cooling era, prior to November 2007, and 151 were born during the cooling era. Among neonates with moderate encephalopathy, the incidence of seizure in cooled infants was less than half the incidence in those not cooled (26% cooling, 61% pre-cooling era; risk ratio = 0.43, 95% confidence interval = 0.30-0.61). Among neonates with severe encephalopathy, there was no difference in the incidence (83% vs 87%; risk ratio = 1.05, 95% confidence interval = 0.78-1.39). These results support animal data and suggest a mechanism by which neonates with moderate encephalopathy can benefit more from cooling than neonates with severe encephalopathy.

Keywords

birth asphyxia, epilepsy, hypoxic-ischemic encephalopathy, incidence, neurocritical care

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Neonatal seizures are common, affecting 1 to 4 neonates per 1000 live term births in the United States.¹⁻⁴ Hypoxic-ischemic encephalopathy is the leading cause of neonatal seizures.² In infants with hypoxic-ischemic encephalopathy, there is increasing evidence that the seizures predict worse outcomes, such as an increased risk of brain injury, cerebral palsy, and epilepsy.⁵⁻¹² Therapeutic hypothermia is the only effective treatment currently available for neonates with hypoxic-ischemic encephalopathy, and has become the standard of care.¹³⁻¹⁹

Although animal studies report anti-seizure effects of hypothermia,²⁰⁻²² clinical evidence presents conflicting results. Meta-analyses of randomized controlled trials fail to show an effect of cooling on seizures in neonates,^{23,24} whereas more recent small, single-center observational studies indicate that therapeutic hypothermia can decrease the incidence of seizure²⁵ and seizure burden.^{26,27} If cooling does in fact reduce seizure incidence, then the clinical implication would be that fewer patients with hypoxic-ischemic encephalopathy would receive potentially harmful²⁸ antiepileptic drugs, whose efficacy is limited.²⁹

The objective of this retrospective cohort study was to examine the relationship between therapeutic hypothermia and cumulative incidence of seizure in neonates with hypoxic-ischemic encephalopathy. We hypothesized that neonates

treated with therapeutic hypothermia are less likely to have seizures than neonates who did not receive the intervention.

Methods

Subjects

Inclusion Criteria. Neonates admitted to the University of California, San Francisco, Intensive Care Nursery from July 2004 to December 2011, who met previously described institutional cooling criteria,³⁰ were included in the study.

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Exclusion Criteria. Subjects were excluded for the following: identification later than 6 hours of birth, birth weight less than 1800 g, coagulopathy with active bleeding, requiring extracorporeal membrane oxygenation (ECMO) prior to 6 hours of life, severe congenital anomalies, syndromes, or known metabolic disorders.

Selection and Group Assignment. The 2004 to 2011 University of California, San Francisco Intensive Care Nursery database, which contained information on all discharged neonates, was compiled prospectively in a systematic manner using a protocol and predetermined variable definitions. The database was continuously sampled for a diagnosis of hypoxic ischemic encephalopathy. Since cooling therapy became available at the study institution on November 1, 2007, neonates born prior to this date were in the “pre-cooling era” group and neonates born on or after this date were in the “cooling era” group. Patients in the cooling era group who did not receive therapeutic hypothermia were excluded after sensitivity analysis showed omission produced similar results.

Measurements

Patient demographic characteristics were extracted from the University of California, San Francisco, Intensive Care Nursery database and chart review. Encephalopathy severity was assigned based on chart documentation of the worst mental status observed during the 7 days following birth. Neonates who were not responsive to arousal maneuvers were designated as having severe encephalopathy and neonates who were hyperalert and/or lethargic were designated as having moderate encephalopathy. Neonates with unclear encephalopathy severity ($n = 16$) due to poor documentation or use of paralytic medication were categorized as having moderate encephalopathy after sensitivity analysis showed that excluding neonates with unclear encephalopathy severity did not qualitatively alter the results. To test the reliability of encephalopathy severity categorization, a second researcher adjudicated this variable for a subset of 20 patients, which resulted in nearly perfect interrater reliability (unweighted kappa = 0.83).

Neonates, who were treated with therapeutic hypothermia, received whole-body cooling via a cooling unit and blanket (CSZ Blanketrol IIITM, CITY). Rectal temperature remained at 33.5° C for 72 consecutive hours. Morphine was given throughout cooling to provide adequate sedation to avoid shivering.

Physician, nursing, transport, and referring hospital notes were reviewed for the presence of seizure prior to hospital discharge. Clinical seizure diagnosis was based on Mizrahi and Kellaway characterizations,³¹ and electrographic seizure diagnosis was based on electroencephalogram (EEG) reports written by neurophysiologists blinded to the study hypothesis. Pre-cooling era seizure monitoring was at the discretion of the treating physician, typically video EEG for 2 hours or less when clinical suspicion of seizure arose. In contrast, cooling era seizure monitoring involved continuous monitoring with both amplitude-integrated electroencephalogram and conventional video EEG applied according to the international 10-20 system, modified for neonates, from the time of admission until the completion of rewarming.^{10,32} Antiepileptic drug treatment was initiated after a suspected seizure, not prophylactically.

Study data were collected and managed using REDCap (Research Electronic Data Capture) tools hosted at University of California, San Francisco.³³ Data were collected with the approval of the University of California, San Francisco, Committee on Human Research.

Analysis

To assess for baseline differences between the groups, the chi-squared and Fisher exact tests were used for comparisons of categorical variables and the *t*- and rank-sum tests were used for continuous variables with parametric and nonparametric distributions, respectively.

The risk of having a seizure was compared between the pre-cooling era group and the cooling-era group, expressed as a risk ratio. Since encephalopathy severity was a priori identified as a confounder, repeat analysis was stratified by encephalopathy severity. The statistical significances of these effects were determined using the chi-squared test. Proportions of seizure diagnoses supported by EEG evidence were compared using the chi-squared test.

For all analyses, *P* values <.05 were considered significant and all tests were 2-sided. Analyses were performed using Stata 12 (Stata-Corp, College Station, TX).

Results

Of 275 neonates diagnosed with hypoxic-ischemic encephalopathy, 224 (81%) met study criteria (Figure 1). Fifty-one patients were excluded for the following reasons: 6 had an hypoxic-ischemic encephalopathy event secondary to postnatal cardiopulmonary arrest, 23 had no documented encephalopathy during the first 6 hours of life, 6 did not meet criteria for perinatal asphyxia, 8 had severe congenital anomalies, syndromes, or known metabolic disorders, 1 had coagulopathy with active bleeding, and 7 did not receive therapeutic hypothermia during the cooling era because of late referral or late recognition. Seventy-three neonates were born during the pre-cooling era and 151 were born during the cooling era. Within the cooling era group, 129 (85%) completed the therapeutic hypothermia protocol and 22 (15%) partially completed the therapeutic hypothermia protocol. Therapeutic hypothermia was stopped for severe cardiopulmonary instability or transition to comfort care. All baseline characteristics, except for sex, were similar between pre-cooling era and cooling era groups. Significantly fewer neonates were treated with phenobarbital in the cooling era compared to the pre-cooling era (Table 1). Of note, among neonates with seizure, 93% (54/58) of cooling era and 96% (45/47) of pre-cooling era neonates were treated with phenobarbital ($P = .6$).

Neonates during the cooling era were less likely to have seizures, diagnosed either clinically or by EEG, than those admitted during the pre-cooling era (risk ratio = 0.60, 95% confidence interval = 0.46-0.78) (Table 2). Among neonates with moderate encephalopathy, those admitted during the cooling era were about half as likely to have seizures as those admitted during the pre-cooling era (risk ratio = 0.43, 95% confidence interval = 0.30-0.61). Meanwhile, no difference in seizure risk occurred among neonates with severe encephalopathy (risk ratio = 1.05, 95% confidence interval = 0.78-1.39).

When excluding subclinical seizures, neonates in the cooling era were about half as likely to be diagnosed with clinical seizures (risk ratio = 0.42, 95% confidence interval = 0.31-0.58). Among neonates with moderate encephalopathy, those in the cooling era were approximately one-third as likely to

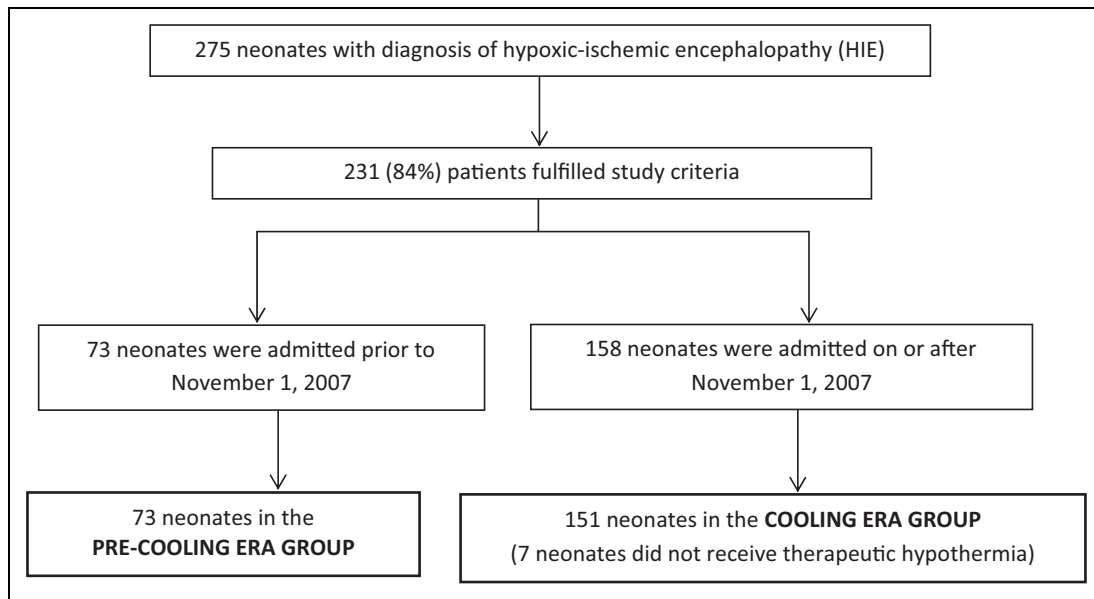


Figure 1. Flow diagram of study selection and group assignments.

Table 1. Characteristics of 224 Neonates With Hypoxic-Ischemic Encephalopathy.^a

	Cooling era (n = 151)	Pre-cooling era (n = 73)	P-value
Male sex	48%	67%	.006
Gestational age, weeks	39.5 (1.5)	39.6 (1.5)	.8
Birth weight, grams	3308 (547)	3424 (618)	.2
Cesarean section	59%	56%	.9
10-minute Apgar score	5 (3-7)	6 (4-7)	.06
Base excess ^b	-18 (6)	-17 (7)	.5
Encephalopathy severity			.5
Moderate	79%	84%	
Severe	21%	16%	
Paralytic medication	4%	8%	.2
Phenobarbital ^c	38%	64%	<.001
ICN length of stay, days	9 (7-12)	11 (6-18)	.4
Death before hospital discharge	16%	15%	.9

Abbreviation: ICN, intensive care nursery.

Values are given in terms of %, mean (standard deviation), or median (25th to 75th percentile).

^aPre-cooling era neonates did not receive therapeutic hypothermia and cooling era neonates received therapeutic hypothermia.

^bBased on worst base excess value from cord gas or first blood gas.

^cAntiepileptic drug treatment was given following a suspected seizure, not prophylactically.

be diagnosed with clinical seizures (risk ratio = 0.27, 95% confidence interval = 0.18-0.43). Neonates with severe encephalopathy, however, did not show a difference in clinical seizure frequency among pre-cooling and cooling era groups (risk ratio = 0.81, 95% confidence interval = 0.57-1.15).

Nearly half (45%) of neonates in the pre-cooling era had at least 1 EEG report available describing a minimum 30-minute duration during the first 4 days of life, whereas all (100%) neonates in the cooling era had at least 1 EEG report available describing continuous EEG monitoring during the period of

hypothermia and rewarming. When analysis was restricted to seizures with an EEG-supported diagnosis, there was no difference in seizure risk among hypothermia-treated neonates (risk ratio = 1.42, 95% confidence interval = 0.83-2.43), nor among the subgroup of neonates with moderate encephalopathy (risk ratio = 0.93, 95% confidence interval = 0.50-1.75). Among neonates with severe encephalopathy, those born in the cooling era were more likely to be diagnosed with electrographic seizures (risk ratio = 3.68, 95% confidence interval = 1.01-13.44). The higher incidence of electrographic seizures in this subgroup was associated with an increased likelihood of detection of subclinical seizures. Among neonates with seizures, not 1 (0/47) patient in the pre-cooling era was diagnosed with only subclinical seizures, whereas 29% (17/58) of patients in the cooling era were diagnosed with only subclinical seizures ($P < .001$).

Discussion

Therapeutic hypothermia was associated with lower incidence of seizure among neonates with hypoxic-ischemic encephalopathy. In spite of increased sensitivity of seizure detection in the cooling era, cooled neonates were about half as likely to be diagnosed with seizures compared to noncooled neonates with moderate encephalopathy, whereas there was no association among neonates with severe encephalopathy. These results support preclinical and clinical studies that suggest that hypothermia has an antiseizure effect in neonates.

Alternatively, these findings may reflect more accurate seizure diagnosis with the advent of continuous EEG monitoring in the cooling era. During the cooling era, fewer clinical spells were diagnosed as seizures, and there was an increased likelihood of diagnosing EEG-confirmed seizures, particularly subclinical seizures. Fewer than half of the subjects in

Table 2. The Proportion of Neonates With Seizures in the Pre-cooling and Cooling Era Groups Stratified by Encephalopathy Severity.

	Cooling era (%)	Pre-cooling era (%)	Risk ratio (95% CI)	P-value
All neonates	n = 151	n = 73		
Any seizure (EEG or clinical)	38	64	0.60 (0.46-0.78)	<.001
Clinical seizure ^a	27	64	0.42 (0.31-0.58)	<.001
EEG-confirmed seizure	27	19	1.42 (0.83-2.43)	.2
Moderate encephalopathy	n = 120	n = 61		
Any seizure (EEG or clinical)	26	61	0.43 (0.30-0.61)	<.001
Clinical seizure ^a	17	61	0.27 (0.18-0.43)	<.001
EEG-confirmed seizure	18	20	0.93 (0.50-1.75)	.8
Severe encephalopathy	n = 31	n = 12		
Any seizure (EEG or clinical)	87	83	1.05 (0.78-1.39)	.8
Clinical seizure ^a	68	83	0.81 (0.57-1.15)	.3
EEG-confirmed seizure	61	17	3.68 (1.01-13.44)	.02

Abbreviations: CI, confidence interval; EEG, electroencephalogram.

^aAny clinical seizure with or without EEG confirmation.

the pre-cooling era had EEG monitoring of any duration, so it is almost certain that the incidence of EEG-confirmed seizures in the pre-cooling era was an underestimate. As a result, our ability to find an association between hypothermia and EEG-confirmed seizures was biased in the direction of showing no association or even a positive association as the data suggest.

Animal studies support that cooling therapy is associated with less epileptiform activity and fewer seizures. According to a fetal sheep model of severe hypoxia-ischemia, cooling was associated with a reduction in the number of epileptiform transients in the first 6 hours after asphyxia insult and a reduction in both early and late seizure amplitude.²⁰ A piglet model showed a significant reduction in the number and duration of electrographic seizures associated with therapeutic hypothermia.²¹ Hypothermia also had anticonvulsant properties in an epilepsy model of rats treated with kainic acid.²² Cooling therapy is believed to protect against neural injury through multiple mechanisms that likely attenuate the excitatory environment in the brain.³⁴ For this reason, these mechanisms can also decrease seizure activity.

Clinical evidence of seizure reduction related to hypothermia is inconclusive. Two meta-analyses of clinical trials, which measured clinical seizures, failed to show an effect of hypothermia.^{23,24} Meanwhile, in a small, observational study from our center, not 1 of 5 neonates with focal stroke who had been treated with hypothermia had seizures, whereas 7/10 (70%) noncooled neonates with focal stroke had seizures.²⁵ In a second single-center observational study, Low et al²⁶ showed that the electrographic seizure burden among 15 cooled neonates was significantly lower than among 16 noncooled neonates. In keeping with our findings, stratification by encephalopathy severity demonstrated that only cooled neonates with moderate encephalopathy had a significant reduction in electrographic seizure burden (49 [26-89] vs 162 [97-262] minutes).²⁶ Using gold-standard electrographic seizure monitoring in both the cooled and noncooled groups, Low et al²⁶ provide evidence for antiseizure benefits of cooling specific to neonates with moderate encephalopathy. Yet their study was not large enough to detect a difference in incidence of seizure, nor were

they able to detect a difference in antiepileptic drug treatment. Most recently, a third study replicated these findings (n = 69), showing reduced electrographic seizure burden (2.2 ± 0.6 vs 7.0 ± 1.0 log units) among cooled neonates with moderate encephalopathy.²⁷ Of note, the lower incidence of electrographic seizure in the moderate encephalopathy groups supports our findings (28% cooled vs 87% noncooled neonates). However, again, the authors did not observe a difference in antiepileptic drug treatment.

Clinical trial data suggest that neonates with moderate encephalopathy benefit the most from cooling. One meta-analysis concluded that death or disability at 18 months was significantly lower among cooled neonates with moderate encephalopathy but not in those with severe encephalopathy,³⁵ whereas another, more recent meta-analysis suggested neonates with severe encephalopathy also benefit but perhaps to a lesser extent.³⁶ If, in fact, hypothermia reduces seizures among neonates with moderate encephalopathy, then 2 potential mechanisms can explain why this subgroup benefits most: less harm due to the seizures, themselves, and less exposure to potentially toxic anticonvulsant medications.

Although our results align well with current animal and clinical evidence, we recognize that this study has limitations related to its retrospective design. First, we note an increase in subjects during the cooling era. If this increase were due to better recognition of subjects with milder injury, the cooling population can have been enriched with subjects that were less likely to have seizures. However, we note that there were similar levels of measurable indicators of severity (10-minute Apgar, base excess, and encephalopathy) in the pre-cooling and cooling eras, and so it is unlikely that selection bias was a factor. Second, as discussed above, improved EEG monitoring and nursing and provider education during the cooling era could have changed the likelihood that bedside nurses and physicians documented and diagnosed clinical events in the absence of EEG correlates as seizures. Third, high-dose anticonvulsant treatment could have led to inappropriate categorization of severe, rather than moderate, encephalopathy in few neonates. This misclassification would result in a less substantial relative

risk among neonates with moderate encephalopathy but would not alter the observed effect among all neonates. Lastly, measurements were based on chart review and, although data extraction was standardized, variation in chart documentation limited our ability to account for all potential confounders. For example, we were unable to account for unmeasured changes in medical management between the pre-cooling and cooling eras, which could mean that the effect we observed between the 2 eras can be associated with secular changes in medical management in addition to or instead of therapeutic hypothermia. Despite these limitations, the central conclusion of the study is upheld by a robust sample size of 224 patients and corresponds with current animal and clinical data.

Conclusion

The results of this study show that cooled neonates with moderate encephalopathy were at lower risk of seizure than noncooled neonates, and continuous EEG monitoring appeared to enhance recognition and diagnosis of seizures. Hypothermia and improved monitoring can contribute to improved neurologic outcomes among cooled neonates with moderate encephalopathy by reducing seizure burden and leading to a decrease in the use of unnecessary anticonvulsant medications. Future studies are necessary to clarify the role of EEG monitoring in this population, as well as the mechanisms underlying reduced seizure risk associated with therapeutic hypothermia and related long-term neurologic outcomes.

Authors' Note

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Author Contributions

SAO contributed to study design, managed the collected data, conducted the initial analyses, and drafted the initial manuscript. MWK designed and managed the University of California, San Francisco, database and along with SLB reviewed and revised the manuscript. SLB and HCG conceptualized the study. HCG contributed to study design and analysis and critically reviewed the manuscript. All authors approved the final manuscript as submitted.

Declaration of Conflicting Interests

The authors declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

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Ethical Approval

Data were collected with the approval of the University of California, San Francisco, Committee on Human Research (approval numbers 10-03702 & 10-02694).

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