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A comparison of levetiracetam and phenobarbital for the treatment of neonatal seizures associated with hypoxic–ischemic encephalopathy

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ABSTRACT

Purpose: Seizures are common in term infants with hypoxic–ischemic encephalopathy (HIE) undergoing therapeutic hypothermia. Although phenobarbital (PHB) is generally considered first-line therapy, some centers have embraced third-generation antiepileptic drugs (AEDs) such as levetiracetam (LEV) given the impression of comparable efficacy and superior tolerability. We set out to compare the efficacy of PHB and LEV in a large single-center cohort.

Methods: We retrospectively identified consecutive newborns with HIE who were monitored with continuous video-electroencephalogram (VEEG) for the duration of therapeutic hypothermia. After identification of seizures, infants were treated with PHB or LEV at the discretion of treating physicians. We assessed time to seizure freedom as a function of AED choice, with adjustment for HIE severity and initial seizure frequency using the Kaplan–Meier procedure and multivariate Cox proportional hazards regression.

Results: We identified 78 infants with HIE. Among 44 (56%) patients who had VEEG-confirmed seizures, 34 became seizure-free during monitoring, and the remaining 10 died. Initial treatment with LEV, in comparison with PHB, predicted a shorter interval to seizure freedom in a univariate analysis (Hazard ratio (HR) = 2.58, $P = 0.007$), even after adjustment for initial seizure frequency and an unbiased ad hoc measure of HIE severity (adjusted HR = 2.57, $P = 0.010$). This effect was recapitulated in an analysis in which patients with treatment crossover were excluded. As expected, severity of HIE was an independent predictor of longer duration to seizure freedom (HR = 0.16, $P < 0.001$) and remained a significant predictor after adjustment for initial seizure burden and treatment agent.

Conclusion: Despite a relatively small sample size and retrospective design, this study suggests that LEV is a viable alternative to PHB in the treatment of neonatal seizures associated with HIE. A large-scale randomized controlled trial is needed to confirm these findings.

1. Introduction

Neonatal hypoxic–ischemic encephalopathy (HIE) is relatively common with an incidence of approximately 1 in 600 live births [1] and accounts for more than one-third of neurologic consultations in the neonatal intensive care unit [2]. Seizures are the most common neurologic sequela of HIE, and they are frequently subclinical or prolonged [3]. Therapeutic hypothermia is the accepted standard of care for treatment of HIE to reduce the likelihood of death and disability [4], and the prompt identification and treatment of concomitant seizures may further improve neurodevelopmental outcomes [5–7].

Although there is no consensus on the ideal treatment of neonatal seizures, phenobarbital (PHB) is by far the most popular first-line treatment [8,9]. However, PHB displays only modest efficacy [10] and has been linked to widespread neuronal apoptosis in the developing brain [11]. Several third-generation antiepileptic drugs (AEDs), and in particular levetiracetam (LEV), have emerged as treatments for neonatal seizures despite a lack of rigorous study [8,12]. In a series of methodologically limited open-label studies, LEV appears to exhibit at least modest efficacy [13–22], and a recent meta-analysis suggests that LEV is at least as effective as PHB [23]. Still, there are no adequately controlled

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trials supporting the use of LEV, though a randomized controlled trial comparing LEV to PHB is underway (clinicaltrials.gov NCT01720667).

Given diverse approaches to treatment of neonatal seizures among physicians at our center and with a large cohort of term newborns with HIE undergoing therapeutic hypothermia and continuous video-electroencephalogram (VEEG) monitoring, we set out to contrast the efficacy of PHB and LEV in the first-line treatment of neonatal seizures.

2. Methods

2.1. Institutional approvals

The use of human subjects and the analyses presented here were approved by the Institutional Review Board at UCLA. The requirement for written informed consent was waived.

2.2. Patients

We retrospectively identified neonates with mild to severe HIE who were admitted to the UCLA Mattel Children's Hospital neonatal intensive care unit with the following inclusion criteria: (1) greater than 36 weeks gestational age, (2) less than 6 h of age, and (3) underwent therapeutic hypothermia with continuous VEEG monitoring. Therapeutic hypothermia was accomplished with either whole body cooling or selective head cooling. The clinical criteria for whole body cooling included a sentinel perinatal event and any one of the following: 10-min Appearance, Pulse, Grimace, Activity, and Respiration (APGAR) score less than or equal to 5, continued need for resuscitation at 10 min after birth, acidosis at less than 1-h age (pH < 7.00, base deficit > 10), and evidence of moderate to severe HIE by neurological exam [24]. For selective head cooling, abnormal amplitude-integrated EEG (aEEG) was required in addition to above clinical criteria [25].

2.3. Cooling procedure

Infants with HIE were cooled for 72 h by using either selective head cooling (Olympic Cool-Cap System, Olympic Medical, Seattle, WA, USA) following standard guidelines [25] or whole body cooling (Blanketrol II Hyper-Hypothermia System, Cincinnati Sub-Zero, Cincinnati, OH, USA) using the procedures set forth by Shankaran and colleagues [24].

2.4. VEEG acquisition and review

Infants were placed on continuous VEEG monitoring by a certified EEG technologist within 6 h of life, with 11 gold-plated electrodes placed according to the modified international 10-20 system. Recordings were accomplished using the Stellate Harmonie acquisition system (Natus Medical, Montreal, Canada). An initial VEEG review was conducted within minutes of first acquisition by a board-certified pediatric electroencephalographer to guide initiation of AEDs. Thereafter, VEEG monitoring continued throughout the duration of cooling and rewarming, or if applicable, until at least 24 h of seizure freedom. All VEEG studies were reviewed clinically at least twice a day, with results relayed to the clinical teams to guide AED management. Antiepileptic drug choice was at the discretion of the treating neurologist or neonatologist. Only infants with VEEG-confirmed seizures were included in our retrospective analysis.

2.5. Seizure data and outcomes

In this study, we specifically considered VEEG-confirmed seizures that were electroclinical or electrographic only (i.e., subclinical) and did not consider clinical seizures without electrographic correlation. For each patient, we recorded the burden of seizures as documented in clinical reports. Initial seizure burden was defined as seizure frequency on the first day of seizures (not necessarily the first day of VEEG recording), and time of seizure freedom was defined as the time after which no further seizures were observed on VEEG. Per protocol, VEEG was recorded for at least 24 h following the last seizure.

2.6. AED exposure

We recorded the timing and dosage of LEV and PHB, as well as AED levels when available. We specifically considered the loading dose of PHB (mg/kg) typically administered over 20 to 60 min, initial dosage of LEV (mg/kg/d; LEV was typically not initiated as a “load”), and the

Table 1
Characteristics of the study population.

	Patients without seizures	PHB first	LEV first	Sig.[a]
Demographics	n = 34	n = 24	n = 20	
Female	15 (44.1%)	9 (37.5%)	6 (30.0%)	NS[b]
Gestational age, weeks[c]	39.0 (37.9–39.7)	38.7 (38.0–39.7)	39.0 (37.5–40.4)	NS
Birth weight, g	3270 (2955–3665)	3376 (3081–3565)	3123 (2837–3461)	NS
Injury characteristics				
Resuscitation measures	n = 34	n = 24	n = 20	
APGAR score, 1 min	1.0 (0.0–2.0)	1.0 (0.0–2.0)	1.0 (0.0–1.0)	NS
APGAR score, 5 min	3.0 (2.0–5.0)	3.0 (1.5–4.0)	3.0 (2.5–4.0)	NS
APGAR score, 10 min	4.0 (3.0–6.0)	5.0 (2.0–6.0)	5.0 (3.0–6.0)	NS
Initial pH	7.1 (7.0–7.3)	7.1 (6.9–7.3)	7.1 (7.0–7.2)	NS
CPR[d]	18 (52.9%)	16 (66.7%)	13 (65.0%)	NS
MRI (n = 66)	n = 30	n = 19	n = 17	
Age at MRI, days		4.7 (4.0–6.0)	7.7 (5.4–10.5)	0.014
Abnormal MRI	16 (53.3%)	14 (73.7%)	12 (70.6%)	NS
Lactate peak on MRS	14 (41.1%)	12 (63.2%)	9 (52.9%)	NS
Seizure measures	–	n = 24	n = 20	
Day 1 seizure frequency, (sz/day)	–	7.0 (4.0–25.0)	16.0 (5.0–61.5)	NS
Severity measures	n = 34	n = 24	n = 20	
Death	6 (17.6%)	9 (37.5%)	1 (5.0%)	0.010
Severity score[e]	2.5 (1.5–3.5)	3.8 (3.0–4.8)	2.5 (2.0–3.75)	0.047
Severity score of at least 3[e]	17 (50.0%)	21 (87.5%)	14 (70.0%)	NS

[a] Comparison between PHB- and LEV-treated patients.
[b] Not statistically significant.
[c] All continuous variables are presented as median (interquartile range) based on nonparametric distributions.
[d] Cardiopulmonary resuscitation (presence or absence of chest compressions and/or use of inotropic agents).
[e] Severity score on a 5-point interval scale with 1 = “very low”, 2 =“ low”, 3 = “moderate”, 4 = “high”, 5 = “very high”, as assigned by raters with knowledge of MRI/MRS findings, APGAR scores, initial blood gas, but blinded to patient identity and all other clinical information including seizure burden and death.