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Short communication

High-Dose Levetiracetam for Neonatal Seizures: A Retrospective Review



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ABSTRACT

Background: Neonatal seizures are frequently encountered in the neonatal intensive care unit and may be associated with serious long-term neurological sequelae. Response to treatment continues to be modest, and treatment guidelines remain unclear. The use of levetiracetam has been on the rise in the past several years due to its favorable safety profile in the face of limited data on its efficacy and optimal dosing regimens. Unlike the older age groups, the benefit of escalating to high-dose levetiracetam of 80-100 mg/kg/day in neonates not responding to the standard used dosing regimen (40-60 mg/kg/day) is not studied. We sought to investigate the safety and efficacy of levetiracetam escalation to high dose regimens for neonatal seizures.

Methods: A retrospective chart review over a 7-year period was conducted at the American University of Beirut to identify neonates with electrographically proven seizures treated with levetiracetam. Data was collected on electroclinical seizure characteristics, underlying etiology, seizure control, other anti-seizure medications, and adverse effects.

Results: Electronic chart review revealed a total of 15 neonates with electrographically confirmed seizures treated with levetiracetam, with escalation to high doses in seven. As a first line drug, levetiracetam monotherapy terminated seizures in six out of 10 neonates, two of whom had complete seizure cessation only after escalation to high doses of 80 or 100 mg/kg/day. When used in combination with other anti-seizure medications, four out of five neonates achieved complete seizure cessation upon escalation to high doses of levetiracetam. No adverse effects were noted.

Conclusions: In neonates not responding to the standard used levetiracetam doses, incremental increases to 80-100 mg/kg/day may be considered. Prospective studies are needed to confirm the promising role of such high dosing regimens, and to better elucidate the role of levetiracetam in neonatal seizures.

1. Introduction

Seizures are common in the neonatal period with an incidence of 1-5 per 1000 term infant [1] and 10-15 per 1000 preterm newborn [2]. Symptomatic of a brain insult in more than 80% of cases [2,3], neonatal seizures are notoriously resistant to anti-seizure medications (ASMs),

and associated with a risk of death and a slew of detrimental neurological consequences including neurodevelopmental delays, epilepsy, intellectual disability and cerebral palsy [3]. The most common etiologies include hypoxic-ischemic encephalopathy (HIE) in term infants [4], and intraventricular hemorrhage (IVH) in preterm neonates [2]. While the harmful effects of the underlying brain insult cannot be

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separated from those attributable to the seizures, a growing body of clinical and preclinical evidence suggests that seizures, in and of themselves, contribute to the adverse neurological sequelae [3,5,6], with the worst neurodevelopmental outcomes occurring in neonates with a high seizure burden [7,8]. However, reducing the seizure burden in this age group remains a serious challenge due to the modest efficacy of currently employed ASMs [9,10], and concerns about their burden on neurodevelopment; a challenge further compounded by the paucity of high quality evidence, especially on the relatively new drugs.

Even though phenobarbital (PHB) is the most commonly used ASM, its modest efficacy [10] and known adverse neurodevelopmental effects in the pediatric age group [11] have prompted many physicians over the last several years to replace this “historical standard” by newer generation medications, namely levetiracetam (LEV). LEV has no known serious acute organ system adverse effects even at the highest used dosing regimens [12], and a benign side effect profile on cognition in children [13]. Compared to PHB, it is therefore less likely to negatively affect neurodevelopment [14]. These safety properties led to the use of LEV in the critical neonatal period, despite the paucity of high-quality evidence [15, 16]. A highly variable LEV efficacy ranging between 30 and 70% has been reported in small studies [17–19], where its use as first line was limited to few patients. In two recent randomized controlled trials in neonates, 24-hour seizure cessation in the LEV treatment arms was achieved in only 28% in one [20], but in up to 86% in another that did not confirm seizures by electroencephalography (EEG) [21]. In neonates, EEG guidance is often required to confirm seizures and their cessation. Except for clonic seizures, it is nearly impossible to confirm epileptic seizures on clinical grounds only [22], let alone the fact that up to two-thirds are clinically silent electrographic seizures [23,24]. In addition, while beneficial escalations above the usual LEV dose of 40–60 mg/kg/day have been reported in the older pediatric age groups, available studies in neonates did not exceed a 60 mg/kg/day dosing regimen [12,25]. In our neonatal intensive care unit (NICU), LEV dose escalation above the usually employed range of 40–60 mg/kg/day is commonly performed. Here we sought to determine whether such relatively high LEV dosing regimens are tolerable and provide additional seizure control in neonates by retrospectively reviewing our cases of neonatal seizures treated with LEV under EEG guidance.

2. Methods

This is a retrospective cohort study of neonates with electrographically confirmed seizures admitted at the NICU of the American University of Beirut Medical Center between June 01, 2012 and February 28, 2019. Approval was obtained from the Institutional Review Board at the American University of Beirut. Neonates with EEGs performed as inpatient during that time period were identified by searching the hospital records. Clinical data as well as EEG reports were obtained by reviewing scanned medical records or electronic health records depending on the period of admission. Neonates were included if they were admitted to the NICU, treated for seizures with LEV, and had electrographically confirmed seizures. All genetic and acquired seizure etiologies (including epilepsy syndromes) were included. Seizures resulting from hypoglycemia or electrolyte imbalance were excluded. Neonates were also excluded if they were diagnosed with seizures without EEG confirmation, or if they received ASMs prior to admission to the NICU without clear documentation of dosage and timing. Data gathered included patient demographics (sex, gestational age, perinatal course), birth history, medical conditions including cardiopulmonary status, organ function (kidney, liver), seizure characteristics (semiology, ictal onset, frequency), seizure etiology, genetic testing, as well as EEG findings and brain imaging results. Collected data concerning ASMs included the sequence of used medications, loading and maintenance doses, adverse events, and drug serum levels when available. The safety profile of LEV at the various dosing regimens was inferred clinically and by comparing organ function prior and after their use.

In our NICU, patients suspected of having seizures, including all patients with HIE treated with therapeutic hypothermia, undergo an urgent initial diagnostic video-EEG of variable durations to confirm seizures, their possible semiology, and their cessation. Neonates with seizures are clinically assessed on a daily basis by the pediatric neurology team, and follow up video-EEGs are also commonly performed within days to weeks of the initial one as deemed necessary to confirm seizure freedom, particularly if seizures are electrographic only or clinically subtle. The type of the first line ASM is at the discretion of the pediatric neurologist. When used, phenobarbital and phenytoin are administered as a load of 20 mg/kg/day followed by an initial maintenance dose of 5 mg/kg/day divided twice daily, and titrated to a free serum level of 15–20 mg/dl. Phenytoin was administered parenterally while phenobarbital was given via the enteral route because its parenteral form is not locally available. Due to the lack of well-established dosing regimens in neonates, the use of LEV varies between practitioners. A loading dose (20–80 mg/kg) may be administered prior to starting the initial LEV maintenance that usually ranges between 40 and 60 mg/kg/day divided two or three times daily. Escalation above this usual standard maintenance dose to high dose LEV (HDL) of 80–100 mg/kg/day is performed with increments of 10–20 mg/kg/day, at variable intervals ranging between hours to days as clinically needed. The HDL regimens were extrapolated from safety data in the older pediatric age groups [12]. Levetiracetam was initially administered via either the enteral or parenteral routes, but switched to the enteral route in all patients few days prior to discharge. When used parenterally, a 100 mg/ml LEV solution was diluted in normal saline or in a 5% dextrose water solution. The resulting solution (10–15 mg/ml) was used within four hours of preparation and administered over a duration of 10–15 minutes. High dose LEV was considered to result in a beneficial response if additional seizure control was achieved upon incremental dose escalations above 60 mg/kg/day, with eventual complete seizure cessation in the absence of any other change in the patient’s treatment regimen.

3. Results

Electronic chart review yielded 15 neonates with electrographically confirmed seizures treated with LEV in the NICU under EEG guidance. There were six girls and nine boys with a median gestational age of 38 weeks (range, 24–40 weeks), and five preterm neonates including two extremely premature (24 and 26 weeks), one very preterm (31 weeks), and three late preterm (36 weeks). There were no identifiable prenatal risk factors for neurodevelopment disorders. Seizures were electroclinical and electrographic in 12 patients, and electrographic only in three, with a mean age of 11.6 days at the time of seizure diagnosis. All patients had a diagnostic video-EEG at the time of the initial assessment, and nine had a follow up study prior to discharge, and within three weeks of the initial one. Video-EEG studies ranged in duration between one and 48 hours. The most common etiologies were HIE in five neonates, and presumed or confirmed neurogenetic conditions and syndromes in seven as summarized in the clinical characteristics and treatment response table (Table 1).

Ten out of 15 neonates received LEV as a first line ASM, with complete seizure cessation in six neonates, of whom, two transiently received phenytoin (PHT) for 24 and 48 hours. In the remaining four patients who received LEV as a first line drug, complete seizure cessation was achieved with one additional ASM including oxcarbazepine (OXC) in two, and PHB in two. In five out of the 15 neonates, LEV was used as a second line following PHB in one patient, and as a third line following a classical combination of PHT and PHB in four, with eventual complete seizure cessation. In all patients, seizure freedom was maintained during the remaining stay in the NICU and at least 72 hours prior to discharge in survivors. All survivors were discharged home on either LEV alone (5 neonates), or a combination of ASMs that included LEV (8 neonates).

The median initial maintenance LEV dose was 40 mg/kg/day and

Table 1

Summary table of the study population characteristics and treatment response. All neonates were seizure free for at least 72 hours prior to discharge, or for the rest of the hospital stay if it extended beyond the neonatal period. Complete seizure cessation was achieved within 1-14 days of anti-seizure medication initiation, and within 1-5 days of the last change in medication regimens in all patients except for two; one with Zellweger disease and one with mitochondrial encephalomyopathy, both of whom achieved seizure cessation three weeks after medication initiation. Escalation to HDL was performed before (*) or after (***) subsequent add-on medications. Only one patient required trials of more than three anti-seizure medications settling on LEV, TPX, and CLZ. (ASMs: anti-seizure medications, CLZ: clonazepam, HDL: high-dose levetiracetam, HIE: hypoxic ischemic encephalopathy, IVH: intraventricular hemorrhage, LEV: levetiracetam, Lt: left, MCA: middle cerebral artery, OXC: oxcarbazepine, PHB: phenobarbital, PHT: phenytoin, Rt: right, TPX: topiramate, W: week). ¹ AD MR: Autosomal dominant mental retardation type 1, ² EIEE: Early infantile epileptic encephalopathy type 25, ³ Mitochondrial myopathy with isolated complex 1 deficiency (by muscle biopsy).

Gestational age (sex)	Age at seizure onset (days)	Underlying etiology	Ictal onset/interictal findings	Semiology	ASM sequence			LEV dosing regimen		Seizure cessation on HDL	Discharge ASM
					1st	2nd	3rd	Loading (mg/kg)	Initial/highest maintenance (mg/kg/day)		
38 W (M)	14	HIE	Rt parietal/suppression	Apnea	LEV			20	30/50		LEV
39 W (F)	1	HIE	Lt central/suppression, discontinuity	Rt hemibody clonic	LEV			40	40/60		LEV
39 W (F)	4	Presumed genetic	Lt temporal/excessive multifocal sharp waves	Apnea	LEV			30	30/60	NA	LEV
39 W (M)	17	HIE	Lt frontal/suppression	Electrographic	LEV			none	25		Deceased (HIE-related multi-organ failure)
37 W (M)	1	HIE	Multifocal/suppression	Electrographic	LEV	PHT (24 hr)		60	60/80	Yes	LEV
36 W (F)	3	Lt MCA stroke	Lt posterior quadrant/normal	Rt hemibody clonic, oromotor automatism	LEV	PHT (48 hr)		30	40/80	Yes	LEV
40 W (F)	2	AD MR ¹ (MBD5 mutation)	Lt central/suppression, discontinuity	Rt hemibody clonic	LEV	PHB		40	60/80**	Yes	LEV, PHB
26 W (F)	58	Bacterial meningoencephalitis	Rt anterior quadrant/suppression	Electrographic	LEV	PHB		none	40/100**	Yes	Deceased (infection-related multi-organ failure)
39 W (M)	4	Presumed genetic	Lt temporal/excessive multifocal sharp waves	Apnea	LEV	PHT	OXC	80	60/100**	Yes	LEV, OXC
38 W (M)	14	Zellweger disease (PEX16 mutation)	Lt and Rt temporal/multifocal spikes	Rt hemibody clonic	LEV	OXC	PHT	80	60/100*	No	LEV, OXC
39 W (M)	2	EIEE ² (SLC13A5 mutation)	Multifocal/multifocal spikes and sharp waves	Rt hemibody clonic, eye uprolling	PHB	LEV	TPX	60	80/100**	Yes	LEV, TPX
36 W (M)	16	Mitochondrial encephalomyopathy ³	Lt frontal/suppression	Apnea	PHT	PHB	LEV	30	40		PHB, LEV
39 W (M)	10	Presumed genetic	Lt and Rt frontal/suppression	Oromotor automatism, blinking, Lt and Rt leg tonic	PHT	PHB	LEV	none	60		LEV, TPX, CLZ
31 W (M)	15	HIE	Rt centro-parietal/excessive multifocal sharp waves	Apnea	PHB	PHT	LEV	none	40	NA	PHB, LEV
24 W (F)	13	IVH	Lt central/excessive multifocal sharp waves, suppression	Rt arm clonic	PHB	PHT	LEV	none	50		PHB, LEV

ranged between 25 and 60 mg/kg/day, except in one neonate who was started on 80 mg/kg/day. A loading dose was administered in 10 out of the 15 neonates, with a median load of 40 mg/kg (range, 20-80 mg/kg). In five neonates, the initial maintenance dose of 25-60 mg/kg/day was not subsequently changed, but further escalation was performed in 10

neonates, reaching 50-60 mg/kg/day in three, and a HDL regimen of 80-100 mg/kg/day in seven. In three patients, escalation to HDL as a first line monotherapy was prompted by an only partial seizure control on the lower dosing regimens. Complete seizure cessation was achieved within 24-48 hours of initiating this escalation in two neonates, but

seizures continued in one patient who required additional ASMs. In the remaining four neonates who received HDL, LEV dose escalation was prompted by an only partial response to polytherapy that included LEV at standard dosing regimens. Complete seizure cessation was achieved within 24–72 hours of initiating this escalation to HDL, and in the absence of any changes to the patients' other ASMs dosing regimens.

There were no adverse side effects in any of the patients, including the five term and two preterm neonates who received HDL. LEV was well tolerated by all patients, and there were no neurological adverse effects. HDL was not discontinued in any of the patients, and no decreases in the dosing regimens had to be performed. There were no serious cardiopulmonary adverse side effects, and no worsening in kidney or liver function tests.

4. Discussion

In this study of mostly term neonates, seven patients received a HDL regimen of 80 or 100 mg/kg/day. Six out of the seven had additional improvements in seizure control with eventual seizure termination when LEV was escalated to HDL above the typically used weight-based range of 40 to 60 mg/kg/day. When used as a first line drug in 10 neonates, the number of those who achieved complete seizure cessation on LEV monotherapy improved from four patients on regular LEV dosing regimens to six upon escalation to HDL. When used in combination with other ASMs, four out of five neonates achieved complete seizure cessation upon escalation to HDL. Such high doses of LEV have not been previously reported in the neonatal literature.

In our center, escalation to HDL is performed when a patient does not respond to the usually used LEV dosing regimens. Seizure termination was attributed to HDL monotherapy in two patients despite the transient use of PHT as a bridge (24–48 hours), since complete seizure cessation was only achieved after LEV dose escalation, and was maintained thereafter on LEV monotherapy. While the contribution of LEV to seizure control cannot be fully ascertained when used with other ASMs, seizure cessation was attributed to HDL in four patients on polytherapy, because escalation to HDL was performed after a lack of response to the other ASMs, and because complete seizure cessation occurred within 24–72 hours of initiating this escalation. In one neonate, the initial maintenance dose of 80 mg/kg/day had to be escalated to 100 mg/kg/day to achieve seizure cessation pointing to an incremental dose-response even at these high doses. This beneficial dose-dependent effect seen in the herein described six neonates who had additional seizure control and eventual complete seizure cessation on HDL suggests that LEV-related seizure improvement does not plateau at 40–60 mg/kg/day. This is in line with the dose-dependent effect of LEV reported with HDL exceeding 100 mg/kg/day in the older pediatric age groups [12,25], and even with increments at the lower dosing ranges from 40 to 60 mg/kg/day in neonates [20]. It is possible that LEV dose optimization, by reaching high doses when clinically indicated, maximizes the number of neonates who may benefit from LEV administration, and such dose-dependent effect may explain the wide ranges of reported efficacy in the neonatal literature [17–20].

Despite the retrospective nature of our study and its relatively small sample size, we noted a more favorable response to LEV in our cohort compared to some prior literature [20], likely due to the benefits of escalation to HDL in a proportion of patients. In the recently published randomized controlled trial by Sharpe et al. [20], electrographically confirmed seizures stopped in only 28% of neonates treated with the usual LEV dosing regimen of 40–60 mg/kg/day. It is noteworthy that in our cohort of 15 neonates treated with LEV at our center, this usual standard dosing regimen failed to terminate seizures in a substantial proportion (seven patients), prompting an escalation to HDL with eventual complete seizure cessation in six patients. This relatively large proportion of neonates who required escalation to HDL in order to achieve seizure cessation suggests that many patients may benefit from incremental increases in LEV above the typically used weight-based

range of 40 to 60 mg/kg/day, and calls for the use of HDL in future prospective studies to better elucidate the full range of LEV efficacy in this age group.

No adverse side effects were reported with HDL or with the lower LEV dosing regimens. LEV was not discontinued in any of the patients due to intolerance or behavioral adverse events. These favorable safety profile results are in line with prior reports on LEV, including HDL at older pediatric ages [12,25]. Even though irritability is well-described in a number of pediatric patients receiving LEV and HDL [12], behavioral changes may not be easily detectable in neonates, especially that they were not specifically sought in this retrospective study. Of note, in two neonates, OXC (20–30 mg/kg/day) in combination with HDL resulted in complete seizure cessation with no adverse effects, suggesting that OXC may be safely used in the neonatal period as previously reported in infants [26].

In conclusion, this is the first study that assesses the use of HDL in neonates. Not only is LEV safe at higher than standard neonatal doses, but it may potentially confer additional seizure control to the usual dosing regimen, as monotherapy or as an adjunct to polytherapy. Escalation to HDL may be considered in neonates not responding to the typically used dosing regimens. Prospective studies are needed to confirm the promising efficacy of HDL, and to potentially levitate the use of LEV in the critical neonatal period of brain development, given its more favorable safety profile compared to other commonly used ASMs such as PHB.

Declaration of Competing Interest

None of the authors has any conflict of interest to disclose.

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