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Original Article

Levetiracetam as the First-line Antiepileptic in Neonatal Seizures

Hari Prasath Ramachandran[1], Jayashree Purkayastha[1*], Leslie Edward Lewis[1], Ramesh Bhat Yellanthoor[1], Apurv Barche[1], Sneha Jaganathan Andrade[1]

1. Pediatrics Department, Kasturba Medical College, Manipal Academy of Higher Education(MAHE), Manipal, Karnataka, India

ABSTRACT

Background: The quest persists for an ideal newer antiepileptic drug (AED) with better efficacy and tolerability. Levetiracetam (LEV) is one of these AEDs with a novel mechanism of action, good pharmacokinetic profile, acceptable tolerability, and side-effect profile. The present study assessed the safety and efficacy of intravenous levetiracetam as a first-line AED in neonatal seizures.

Methods: This prospective observational study was conducted on all term neonates with seizures admitted to the Neonatal Intensive Care Unit (NICU) of a tertiary care center. Neonates with hypoglycemia, hypocalcemia, hypomagnesemia, inborn errors of metabolism, or those who received other AEDs prior to admission were excluded from the study. 20mg/kg Intravenous LEV was administered as first-line AED and graded up to 40mg/kg if seizures were not controlled in 2 h; thereafter, second-line AED was added.

Results: Only 36.2% (21/58) of the cases responded to LEV as first-line AED. Hypoxic Ischaemic Encephalopathy(HIE) was the most common etiology of seizures (55.2%). Subtle seizures were most responsive to LEV (60%), while multifocal clonic seizures (22.3%) responded the least. No adverse effect of LEV was observed during the study period.

Conclusion: Only 36.2% of the cases responded to LEV as first-line AED, and subtle seizures were the most responsive seizures. Therefore, the efficacy of LEV as first-line AED in neonatal seizures is yet to be proven by a larger study. There were no adverse effects of LEV during the study period indicating the relative safety of this drug.

Keywords: Levetiracetam, Response, Side effects, Seizures, Term neonates

Introduction

Neonatal seizures can be defined as a paroxysmal alteration in behavioral, motor, or autonomic function resulting from the abnormal electrical activity of the brain in the neonatal period. It represents one of the most common neurological disorders in newborns resulting from prenatal, perinatal, or postnatal involvement of the central nervous system (CNS) (1). The immaturity of the developing brain of a neonate, along with the still-evolving neurological mechanisms, including varying receptor distribution, as well as mature and immature neuroprotective mechanisms, predisposes the neonate to seizures (2). Seizures are typically the only symptom of underlying brain pathology and may herald subsequent epilepsy. They are frequently associated with a metabolic disorder or represent a sign of CNS infection. Accordingly, neonatal seizures are responsible for long term neurodevelopmental outcomes, especially motor deficits, cognitive deficits, intellectual impairment, cerebral palsy, seizure disorder, or overlap of any of the above-mentioned problems, as well as high mortality (3, 4). Despite years of rich scientific experience, research, and advancements, no medication currently used in the treatment of neonatal seizures has demonstrated superior efficacy in seizure control or in terms of better neurodevelopmental outcome (5).

In fact, the harms of old-generation AED santiepileptic drugs may outweigh the benefits considering the neuronal apoptosis they induce

* *Corresponding author*: Jayashree Purkayastha, Pediatrics Department, Kasturba Medical College, Manipal Academy of Higher Education (MAHE), Manipal, Karnataka, India. Tel: +919886249133; Email: jayashreepurkayastha@yahoo.com

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(6). In the wake of such circumstances, even after so many years, the quest for an ideal newer antiepileptic drug with a novel mechanism of action and better efficacy and tolerability still continues. Levetiracetam (LEV) with a novel mechanism of action, good pharmacokinetic profile, acceptable tolerability, and side-effect profile is currently used off-label by many for neonatal seizures across the world (7). LEV is a pyrrolidine derivative antiepileptic that binds to the synaptic vesicle protein SV2a which is expressed throughout the brain. LEV binding to SV2a impedes neurotransmitter release and vesicle transport within the neuron. SV2a receptor appears to be important in both partial and generalized seizure disorders. Targeting the SV2a protein is unique to LEV providing a novel mechanism of action for neonatal patients (8). The most commonly observed side effects of this medication are somnolence and behavioral changes. Due to the limited side effect profile and drug interactions of LEV, routine monitoring is not necessary in the majority of cases. LEV has recently been recommended by pediatric neurologists for neonatal seizure control due to its favorable pharmacokinetic profile extrapolated from older children and neonatal pharmacokinetic studies. Based on the literature review, LEV appears to be safe and effective in the treatment of several types of neonatal seizures; nonetheless, there is no robust evidence of its application as a first-line agent or monotherapy (8).

Therefore, the present study aimed to assess the safety and efficacy of intravenous Levetiracetam as a first-line antiepileptic medication in neonatal seizures.

Methods

The current prospective observational research was conducted on all neonates ≥ 37weeks (inborn and outborn) with neonatal seizures admitted to Neonatal Intensive Care Unit (NICU) of a tertiary care center of South India within October 2015 to May 2017.

Approval for the study methodology, consent process, and pre-validated proforma was obtained from the Institutional Ethics Committee. (IEC 638/2015)

Inclusion criteria: All term neonates with seizures admitted to NICU were included in the study. Exclusion Criteria: Neonatal seizures due to metabolic causes, such as hypoglycemia, hypocalcemia, hypomagnesemia, and inborn errors of metabolism, as well as neonates on other antiepileptic drugs (AEDs) prior to inclusion into the study.

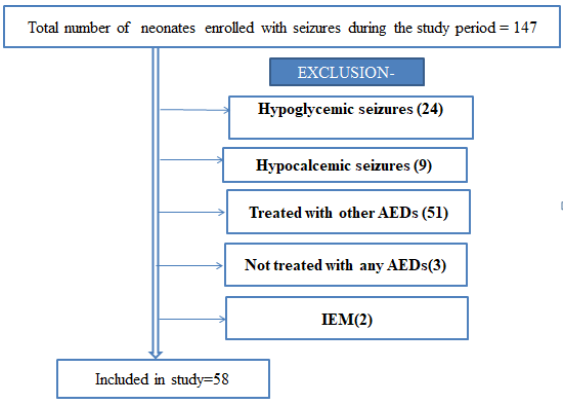

Figure 1. Study flow chart

Informed written consent was obtained from the parents and/or guardians.

Figure1. shows the study flow chart. The demographic data included gender, gestational age, mode of delivery, resuscitation details, birth weight, as well as maternal and perinatal history. History regarding seizure semiology, treatment details (if any), physical examination findings, and neurological system examination findings were recorded in the pre-validated proforma predesigned for the study. Baseline investigations were performed to rule out metabolic causes, such as hypoglycemia and hypocalcemia. Neonates were administered intravenous (IV) LEV as first-line anti-epileptic (AED) as per the discretion of treating neonatologists. All neonates with seizures admitted to the NICU during the study period received IV LEV as first-line AED, except for those who had hypoglycemia, hypocalcemia, hypomagnesemia, those with suspected inborn errors of metabolism from family history, and those who received other AED from outside. Therefore, there was no observed bias, and the facilitator was the chief neonatologist in the NICU.IV Levetiracetam-loading dose of 20mg/Kg was administered. If seizures were not controlled with 20mg/Kg, the dose was increased up to a maximum of 40 mg/Kg/day in increments of 10mg/kg. If the seizure was still not controlled within a maximum of 2 h, an alternative AED was given. If seizures were controlled with LEV, the maintenance dose of IV LEV 10 mg/kg/dose diluted in 15 ml 5% Dextrose every 12th hourly was given as an infusion over 15 min and monitored. Ethylenediaminetetraacetic acid (EDTA) and heparinized blood samples of 0.5ml were drawn through clean venipuncture from the neonates on admission and the 3rd day of hospital stay. They were analyzed for serum AST/ALT (UV with P5P

method/ Hitachi Cobas c 501 system), blood urea (Urease glutamate dehydrogenase method by using Roche/ Hitachi Cobas c 501 system), Serum creatinine (Jaffe's test method by using Roche/Hitachi Cobas c 501 system) Platelet count(Beckman Coulter LH780). Due to the limited side effect profile and wide therapeutic window, LEV serum levels were not monitored.

Some investigations, such as ultrasound of the brain, brain electroencephalography (EEG), and Magnetic Resonance Imaging (MRI), were performed as clinically indicated during the course of hospital stay. Neonates were constantly monitored for variations in vital parameters, including heart rate, blood pressure (BP), temperature, urine output. They were followed up until 3 months of age for any neurological deficits, seizures, and side effects. The outcome was measured in terms of any neurodevelopmental impairment, microcephaly, and recurrence of seizures.

The data were analyzed in SPSS software (version 21). Descriptive data were expressed as percentages, medians, interquartile ranges, means, and standard deviations.

Results

In our study population, the mean gestational age was reported as 38.9±1.01 weeks, and mean birth weight was 2846±492 grams (Table 1). Among the 58 neonates under study, 36 (62.1%) cases presented with seizures with onset within 48 h after birth, while 22 (37.9%) subjects had seizures with onset after 48 h of age. Table 2 depicts the seizure etiology and response to LEV. Hypoxic-ischemic encephalopathy (HIE) was the most common etiology of seizures (55.2%). The exact cause of seizures could not be found in about

Table 1. Demographic information

Variable (n=58)		n	Percentage
Gender:	Male	41	70.7%
	Female	17	29.3%
Place of birth	Inborn	11	18.9%
	Outborn	47	81.1%
Period of Gestation	37w -37w6d	11	18.9%
	38w- 38w6d	17	29.4%
	39w- 39w6d	22	37.9%
	40+ weeks	8	13.8%
Parity index	Primi gravida	32	55.2%
	Multi gravida	26	44.8%
Birth weight	NBW (≥2.5kg)	47	81.1 %
	LBW (<2.5kg)	11	18.9 %
Mode of delivery	Vaginal delivery	30	51.7%
	C - section	28	48.3%

(Abbreviations: NBW: normal birth weight, LBW: low birthweight)

Table 2. Relationship between etiology and seizure control with levetiracetam

Etiology n=58	Seizure control-Dose					
	20mg/kg(n=13)		30mg/kg(n=7)		40mg/kg(n=38)	
	Controlled	Not controlled	Controlled	Not controlled	Controlled	Not controlled
HIE-II (n=24)	5		4		1	14
HIE-III (n= 8)		1	1			6
Polycythemia (n=5)	1				1	3
Cerebral malformations (n=3)	2					1
Meningitis (n=2)	1					1
Idiopathic (n= 16)	3		2			11
Total	12	1	7		2	36

Table 3. Relationship between seizure semiology and levetiracetam

Semiology n=58	Seizure control-Dose					
	20mg/kg(n=13		30mg/kg(n=7)		40mg/kg(n=38)	
	Controlled	Not controlled	Controlled	Not controlled	Controlled	Not controlled
Subtle (n=10)	4		1		1	4
Focal Clonic (n=7)	3					4
Multifocal Clonic (n=27)	1	1	5			20
Generalised Tonic (n=14)	4		1		1	8

16 neonates (27.5%), Polycythemia (5/58), cerebral malformations (3/58), and Meningitis (2/58), respectively, constituted 8.6%, 5.2%, and 3.5% of the remaining neonates with seizures. Among all the neonates with HIE, 34.3% of cases responded to LEV. Out of 24 cases of HIE stage II, 41.6% responded to LEV, while out of 8 cases of HIE stage III, only 12.5% responded to LEV. In addition, among neonates with seizures secondary to polycythemia, 2/5(40%) responded to LEV. Cerebral malformations showed a 66.6% response to LEV (2/3), whereas Meningitis demonstrated a 50% response (1/2) to LEV. Idiopathic seizures were observed to have 31.3% seizure control with LEV.

In the current study, the multifocal clonic seizure was the most commonly observed type of seizures (46.5%), followed by generalized tonic seizure (24%), subtle seizures (17.3%), and focal clonic seizures (12%). Table 3 depicts the LEV response and seizure semiology. Multifocal clonic seizures showed a 22.3% response, while generalized tonic seizure demonstrated a 42.8% response. Subtle seizures were successfully controlled with LEV in 60% of the cases.

IV LEV administered as first-line AED was found efficacious in controlling seizures in only 21(36.2%) cases (Table 4). A number of 12 neonates achieved seizure control with 20mg/kg of Levetiracetam, whereas 1 more neonate who initially achieved seizure control with 20mg/kg of Levetiracetam had recurrence at 96 h; therefore, it was considered a failure. Seven neonates achieved seizure control with 30mg/kg of Levetiracetam. Out of 38 cases who required administration of 40mg/kg of Levetiracetam, only 2 cases achieved seizure control, while the other 36 newborns required an alternative second-line AED for seizure control. Out of 58 neonates studied, 37(63.8%) cases required an alternative second-line AED, out of whom 10(17.2%) subjects required a third AED. In addition, out of 58 neonates, one subject did not respond to multiple AEDs, and pyridoxine was administered and responded to seizures.

In our study, ultrasound of the brain (as per clinical discretion) was performed for 33 neonates, among whom 20 cases had no notable abnormal findings. Mild-moderate abnormalities (IVH grade I/II, periventricular flaring) were noted in 9 (27.3%) cases while 4(12.1%) subjects had severe abnormalities (IVH grade III/IV, malformations). There was no relationship between the ultrasound brain findings and seizure response to LEV. Table 5. depicts MRI findings and responses to LEV.

In this study, out of 58 neonates, 37 cases underwent MRI (as per clinical discretion), and 54% of neonates were found to have severe abnormalities- Global pattern (diffuse cortical and/or subcortical involvement), periventricular leukomalacia, cystic encephalomalacia, BGT pattern(thalamic and/or basal ganglia, PLIC-Posterior Limb of Internal Capsule involvement), Hemorrhage (IVH-grade III/IV, SDH). Moreover, 29.8% of subjects had moderate abnormalities-Hemorrhage (SAH, Subgaleal hematoma), Watershed pattern-(parieto-occipital region

Table 4. Levetiracetam efficacy as first-line anticonvulsant

Levetiracetam Dose (n=58)	Controlled	Not controlled
20mg/kg	12	1
30mg/kg	7	0
40mg/kg	2	36
Total	21 (36.2%)	37 (63.8%)

Table 5. Magnetic resonance imaging and seizure control with levetiracetam

Grade	Effect	MRI(n=37)	
		n	%
No Abnormality	Controlled	1	2.7
	Not controlled	5	13.5
Moderately Abnormal	Controlled	4	10.8
	Not controlled	7	18.9
Severely Abnormal	Controlled	9	24.3
	Not controlled	11	29.8

involvement), while 16.2% of cases had no abnormalities on MRI. In the present study, neonates with severely abnormal MRI findings showed 45% (9/20) seizure control with LEV, whereas 84% (5/6) of subjects whose MRI findings demonstrated no abnormalities did not respond to LEV.

Furthermore, in the current study, EEGs were conducted as per clinical discretion, within the first week of onset of seizures and observed that EEGs picked up 22.3% severe abnormalities (markedly discontinuous background activity, severely decreased voltage, burst suppression pattern, prolonged inter-burst interval (>20 seconds), excessive sharp waves-positive vertex or Rolandic, positive frontal and negative occipital sharp waves, focal lateralized epileptiform discharges) and 11.1% moderate abnormalities (voltage asymmetries and delayed maturation of background activities), while 66.7% of neonates had no detectable EEG abnormalities after 1 week of treatment initiation. In addition, no relationship was detected between EEG abnormality and response to LEV in this study.

Among the 58 neonates studied, 7 expired and 4 were lost for follow up. Out of the remaining 47 subjects, 25 cases were discharged while prescribed LEV alone, 5 cases were discharged with multiple AEDs, including LEV, 6 and 3 neonates with only phenobarbitone and phenytoin, respectively, while 1 newborn was discharged while prescribed pyridoxine and seven subjects were discharged without any AEDs.

Out of them, three neonates were observed to have a seizure at follow up at 3 months of age, one of whom was on LEV maintenance, while the other two were not on any AEDs.

One neonate had microcephaly and spasticity, HIE stage III follow up on LEV maintenance, and two other newborns who were not on any AEDs and were follow up cases of HIE stage I had myoclonic twitches. Nonetheless, no developmental delay was observed in any other neonate using the clinical examination.

Biochemical and Laboratory parameters (Urea, Creatinine, AST, ALT, Platelet counts) performed on days 1 and 3 of receiving LEV were within normal limits, and no significant adverse effects were observed during the study period.

Among the 58 neonates studied, 7 cases expired and 51 subjects survived. The seven cases who expired had HIE stage III (3/7), HIE stage II (2/7), Meningitis (1/7), sepsis-induced acute kidney injury, or hypoxic seizures (1/7).

Discussion

In their study, Ramantani et al. (9) found HIE (38%) and cerebral hemorrhage (38%) to be the most common cause of seizures in term neonates. Segidhi et al. (10) reported idiopathic seizures as the most common type (68%), followed by meningitis (14%), HIE in only 6%, IEM in 6%, as well as withdrawal syndrome, and kernicterus contributing to 2% and 4 % respectively. In this study, the most common cause of seizures was HIE (55.2%), followed by idiopathic seizures (27.5%). Seizures most responsive to LEV in our study were cerebral malformations (66%) and least responsive to LEV were HIE stage III (12.5%). In a study conducted by Khan et al., out of 22 neonates enrolled, 12 cases were found to have HIE. Out of these neonates, 11 cases achieved seizure control with Levetiracetam but not as a first-line medication (11).

In a study performed by Segidhi et al. (10), out of 50 cases administered with Levetiracetam as first-line AED, 40 cases required phenobarbitone titration, and 3 subjects required additional phenytoin in order to achieve seizure control.

Out of 38 neonates studied by Ramantani et al. (9), 19 cases required titration with phenobarbitone, and 3 subjects required phenobarbitone as second-line AED. Segidhi et al. (10), carried out a study on 50 neonates and reported that tonic seizures (46%) were the most commonly observed type of seizures, followed by subtle and clonic seizures (each 20%), myoclonic seizures(10%) and spasm(4%). In their study conducted on 13 term neonates, Ramantani et al. (9) found focal clonic seizures(38%) to be the most prevalent form, followed by focal tonic(23%), subtle, generalized tonic, and myoclonic (15% each), with multifocal clonic being the least commonly observed form of seizures(8%). In our study, the most common type of seizures was multifocal clonic (46.5%), followed by generalized tonic reported as 24%. Seizures most responsive to LEV were subtle seizures (60%), while multifocal clonic seizures were the least responsive to LEV as a first-line AED (22.3%).

A study conducted by Malik et al. (12), reported that 10% of newborns with neonatal seizures had an abnormal finding on cranial ultrasound, while another study performed by Alcover-Bloch et al. (13), reported 43% incidence of abnormal findings in cranial ultrasound of neonates with seizures.

Ramantani et al. (9) denoted that out of the term neonates with seizures, 8% of cases had no

abnormalities, while 30% and 62% of subjects had moderate and severe abnormalities in cerebral ultrasound, respectively. Segidhi et al. evaluated the ultrasound findings and reported the following results: normal findings in 36 cases (72%), intracranial hemorrhage (16%), Hydrocephaly (3%), both intracranial hemorrhage and hydrocephalus (2%), and brain cyst (4%) (10).

However, in the present study, it was observed that the response of seizures to Levetiracetam could not be determined based on ultrasound findings.

In line with our observation, WHO guidelines on neonatal seizures specify that neuroimaging does not help in determining the response to AEDs (14).

A study conducted by Rollins et al. indicated that "in term neonates with seizures, MRI findings did not correlate with either clinical signs of perinatal distress or perinatal causes of brain injury" (15). In a similar vein, another study performed by Miller et al. noted that "severity of seizures in newborns with perinatal asphyxia is independently associated with brain injury and is not limited to damage detectable by MRI (16). In this study, no relationship was detected between abnormal MRI and response to LEV as the first-line AED.

In this study, 22.3% of cases had severe EEG abnormalities, 11.1% had moderate abnormalities, while 66.7% had no detectable abnormalities after 1 week of initiation of LEV. Our limitation was that we did not perform baseline EEG within 24-48 h after seizure onset. In agreement with the current study, according to Segidhi et al. (10), 76% of EEGs performed at 1 week after drug initiation was normal with 96% of follow-up EEGs being normal.

In the study by Ramantani et al. (9), 5(38%) cases recorded severe abnormalities in EEG background activity, while 5(38%) subjects were normal, and 3(24%) cases showed moderate abnormalities. Out of 10 subjects with moderate and severe abnormalities, 5(50%) cases showed normalization at 1 week after treatment initiation. Some prospective studies (17, 18) noted that "the use of EEG could help with the anticonvulsant management"; nonetheless, another study conducted by Connell et al. (19) demonstrated "mixed results in this regard". Similar to the observations made in the study by Connell et al., the relationship between electrographic seizures and AED management is ambiguous in the present study (19).

Segidhi et al. (10) have found that LEV was able to control seizures in 47/50 neonates at the end of 1 week; however, phenobarbitone titration during the first 24 h was required in 40/50 neonates. Out of 38 neonates studied by Ramantani et al. (9), 8 cases required phenobarbitone as the second-line AED. Out of the remaining 30 subjects who received LEV, 19 cases were put on phenobarbitone titration up to 24 h, and 10 subjects required further phenobarbitone titration during the first week. Seizure control was achieved in all of these neonates at the end of 1 week. In our study, seizure control was achieved in 21(36.2%) cases with LEV loading dose as the first-line antiepileptic. Seizure control was achieved within 2 h of the loading dose of LEV. The 37 non-responders received the second-line AEDs, namely phenobarbitone or phenytoin.

Ramantani et al. (9) followed up their cases for up to 12 months after treatment and assessed them twice at an interval of 6 months. They found that among 12 term neonates with seizures, 2 cases had post-neonatal epilepsy(17%) and 5 subjects had a developmental delay (42%) at 6 months of age. Moreover, when assessed at 12 months of age, 2 (17%)cases had post-neonatal epilepsy and 3(25%) subjects had persistent developmental delay (8). We assessed the neonates at 3 months of age and found that one case had seizures, sequelae of HIE stage III, while the other two subjects had myoclonic seizures sequelae of HIE stage II.

In accordance with the results of the present study, in their study, Ramanatani et al, Falsaperia et al., and Abend et al. observed that there was no derangement in biochemical and lab parameters due to LEV (9, 20, 21).

The strength of the current study included 1) the exclusive use of Levetiracetam as the first-line AED in seizure control without titration with other drugs, 2) continuous and meticulous monitoring of the neonates for any adverse effect.

The remarkable limitations of the study entailed small sample size, non-performance of baseline EEG, and follow-up at 3 months of age which is too early for neurodevelopmental assessment.

Conclusion

In the present study, 36.2% of neonatal seizures responded to Levetiracetam as first-line AED, 63.8% of the cases required a second-line AED. Subtle seizures were better controlled (60%) with LEV in our study. LEV exerted no adverse effects during the hospital stay and within 3 months of follow up. Moreover, EEG and MRI

showed no relationship with the response of seizures to Levetiracetam in the current study. Further research with large sample size is required to study the efficacy and safety of Levetiracetam as first-line AED in neonatal seizures.

Acknowledgments

None.

Conflicts of interest

The authors declare that they have no conflict of interest regarding the publication of the current article.

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