Original Article

Intravenous Levetiracetam for Treatment of Seizures in Term and Preterm Neonates

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ABSTRACT

Context: Seizures are the most frequent neurological disturbance in the neonatal period, and there are no evidence-based guidelines for the treatment of neonatal seizures. Here we report a study on the use of levetiracetam as second-line therapy in the treatment of seizures in term and preterm neonates. Aim: The aim of this study was to assess the efficacy and safety of levetiracetam for seizures of term and preterm neonates. Settings and Design: We retrospectively analyzed data of the patients who had seizures and who were treated with levetiracetam as an add-on therapy to phenobarbital during the neonatal period. Statistical Analysis: The Statistical Package for the Social Sciences (SPSS) software, version 15.0 (SPSS, Chicago, Illinois), was used for statistical analysis. Continuous variables were expressed as mean values and standard deviations. Results: Thirty-six patients (8 term and 28 preterm) received levetiracetam. Mean dose of levetiracetam was 31.67 ± 14.83 mg/kg/day. Twenty-five of the patients (69.4%) were seizure free with levetiracetam treatment. Electroencephalography recordings improved in 28 (77.8%) of the patients after levetiracetam. No severe adverse effects were observed. Conclusion: Our data suggest that levetiracetam may be a safe and effective treatment for neonatal seizures, which are unresponsive to phenobarbital.

KEYWORDS: Levetiracetam, neonatal convulsions, neonatal seizures, neonates, treatment

INTRODUCTION

Seizures are the most frequent neurological disturbance in the neonatal period, occurring 1–3 per 1000 live births in term infants and 10 times more in preterm infants.[1] Hypoxic–ischemic encephalopathy, stroke, cerebral malformations, central nervous system infections, and metabolic disturbances are the most common causes of neonatal seizures in term infants, whereas in preterm infants, intraventricular hemorrhage is the main underlying etiology.[2,3] Neonatal seizures are observed very early in life, mostly within the 1st day and 1st week.[1] They may harm the developing brain and cause adverse neurological outcome.[4] There are no evidence-based guidelines for the treatment of neonatal seizures.[5]

Phenobarbital is the most common first-line drug used to manage neonatal seizures.[6] However, it can control seizures only in 40%–50% of cases after a loading dose and in 70% after repeating loading doses.[7,8] When seizures are not responsive to phenobarbital, second-line drugs are needed. Phenytoin and midazolam are most commonly used second-line drugs.[10] Levetiracetam has been reported as a first- and second-line treatment for seizure management in preterm and term neonates.[11-19] It has been used in children and adults with good efficacy and safety profile.[10] It has a broad spectrum of antiepileptic activity.[6] It does not increase apoptosis in developing rodent brain, and it

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Levetiracetam decreases neurodegeneration in hypoxia–ischemia models of rodents.\(^{[21-23]}\) Levetiracetam is approved as an adjunctive treatment for partial-onset seizures in infants and children from 1 month of age by the US Food and Drug Administration but not for the neonatal age-group.\(^{[24]}\) Levetiracetam is studied on small groups of neonates, and data are limited for its routine usage in neonates, especially in preterm infants. Here, we report our experience about intravenous levetiracetam treatment in term and preterm neonates. The aim of this study was to assess the efficacy and safety of levetiracetam for seizures of term and preterm neonates.

**Materials and Methods**

The study was a retrospective review of patients who had seizures and who were treated with levetiracetam during the neonatal period in Dokuz Eylül University Neonatal Intensive Care Unit, Izmir, Turkey. The study was approved by the institutional ethics committee. Clinical data were obtained from patient’s medical records. Progress notes of neonatologists and pediatric neurologists, laboratory and radiologic test results, and electroencephalography (EEG) recordings were evaluated. Patient’s gender, gestational age, birth weight, type of delivery, semiology of seizures, etiology of seizures, age at seizure onset, neurological examination, results of cranial imaging, antiepileptic drug names and doses, response to treatment, adverse effects, and examination during follow-up visits were noted.

Seizures were classified as subtle, focal clonic, multifocal clonic, focal tonic, generalized tonic, and myoclonic.\(^{[25]}\)

In the neonatal intensive care unit, infants had first received phenobarbital as first-line treatment and then levetiracetam as second-line. Patients with phenobarbital unresponsive seizures had received intravenous levetiracetam at a loading dose of 10 mg/kg and maintained on a dose of 10 mg/kg/day. In some patients, whose seizures had continued after first loading, levetiracetam had been titrated up to 60 mg/kg/day. EEG recordings were obtained after the first seizure and after levetiracetam treatment. They were performed bedside in neonatal intensive care unit. EEG recordings were reviewed and classified as (1) normal or mild abnormalities: normal pattern for gestational age, including slightly abnormal activity, for example, mild asymmetry and mild voltage depression; (2) moderate abnormalities: discontinuous activity with interburst interval too long for gestational age, clear asymmetry or asynchrony, and absence of age-appropriate EEG features; and (3) major abnormalities: severe discontinuity in EEG for gestational age, burst suppression pattern, no appropriate sleep-wake cycle for gestational age, and multifocal sharp waves.\(^{[17]}\) Improvement on EEG was defined as a 50% or more decrease or disappearance of epileptiform discharges.\(^{[13]}\)

Cerebral ultrasonographies were classified as (1) normal: no pathology; (2) moderately abnormal: grade 1 or 2 intraventricular hemorrhage, mild ventriculomegaly, and periventricular echodensities; and (3) severely abnormal: grade 3 and 4 intraventricular hemorrhage, cystic periventricular leukomalacia, and malformation.\(^{[17]}\) Neurologic examination was evaluated as (1) normal: normal muscle tone, active muscle movements, and normal alertness for age; (2) mildly abnormal: hypertonia and hyperexcitability; (3) moderately abnormal: hypotonia or hypertonia, decreased muscle movements, and lethargy; and (4) severely abnormal: flaccid, inactive, and coma.\(^{[17]}\) The Statistical Package for the Social Sciences (SPSS) software, version 15.0 (SPSS, Chicago, Illinois), was used for statistical analysis. Continuous variables were expressed as mean values and standard deviations.

**Results**

In this study, 36 neonates (8 term and 28 preterm) who had received levetiracetam as a second-line agent for seizure control were analyzed. There were 15 (41.7%) females and 21 (58.3%) males. Seventeen (47.2%) of them were born <28th gestational weeks, 11 (30.6%) were between ≥28 and 37 weeks, and 8 (22.2%) were term neonates (≥38 weeks). The mean gestational age was 30 ± 5.72 weeks. The mean birth weight was 1.604 ± 1.066 kg. Eight neonates (22.2%) had a diagnosis of hypoxic–ischemic encephalopathy, 11 (30.6%) had intraventricular hemorrhages, 10 (27.8%) had prematurity-related problems (respiratory distress syndrome), 4 (11.1%) had sepsis, and 2 (5.6%) had metabolic disorders, propionic acidemia and methylmalonic academia. Etiology in one patient was not identified. Twenty-three (63.9%) patients had multifocal clonic, 6 (16.7%) had subtle, 3 (8.3%) had focal clonic, 2 (5.6%) had generalized tonic, 1 had (2.8%) focal tonic, and 1 had (2.8%) myoclonic seizures. Clinical data of all infants are summarized in Table 1.

EEG recordings had been evaluated after the first seizure and after levetiracetam treatment. The first EEGs showed major abnormalities in 12 (33.3%), moderate abnormalities in 13 (36.1%), and normal or mild abnormalities in 11 (30.6%) patients. Cerebral ultrasonographies were normal in 12 (33.3%) and abnormal in 24 (66.7%) patients. Thirteen (36.1%)
patients had moderately abnormal and 11 (30.6%) had severely abnormal cerebral ultrasonography.

Response to treatment was determined clinically and electrophysiologically. The mean dose of levetiracetam was 31.67 ± 14.83 mg/kg/day. Twenty-five (69.4%) patients were seizure free in 72 h. Eleven (30.6%) needed a third-line antiepileptic drug for seizure control. It is unclear whether levetiracetam decreased the seizure frequency in the neonates that required a third-line drug given the lack of documentation. EEG recordings improved in 28 (77.8%) patients after levetiracetam treatment. Levetiracetam controlled seizures in 13 of 17 (76.5%) neonates <28 weeks, in 7 of 11 (63.6%) neonates between 28–37 weeks, and in 5 of 8 (62.5%) term neonates [Table 2].

Levetiracetam was tolerated well in our study group. No serious side effects were evident during or after the infusion of levetiracetam. Vital signs of the patients did not change during the infusion. One patient had neutropenia (white blood cell count: 3900/mm³) and another had agranulocytosis (hemoglobin: 9.1 g/dL, white blood cell count: 3400/mm³, and platelet count: 9200/mm³) during maintenance treatment with no signs of infection. But this could not be clearly attributed to levetiracetam, as these patients were also receiving phenobarbital. Levetiracetam and phenobarbital were
discontinued in these patients, and white blood cell counts turned to normal in 2 weeks.

The mean duration of levetiracetam use was 124.44 ± 127.39 days. Levetiracetam was administered by intravenous route during loading. The duration of the intravenous treatment for each patient is unknown given the lack of documentation. Twenty-four (66.7%) patients were followed up after discharge from neonatal intensive care unit. Among 24 patients who had been followed, 11 (30.6%) had been using oral levetiracetam at last follow-up visit and were seizure free. Among the patients with follow-up, neurologic examination was normal in 12 (50%). No side effect was reported during follow-up visits.

**DISCUSSION**

Therapeutic options for neonatal seizures are limited. Phenobarbital, which acts through gamma-aminobutyric acid-ergic (GABAergic) mechanisms, still remains as the most frequently used antiepileptic drug for the treatment of neonatal seizures. Efficacy of phenobarbital for neonatal seizures is reported to be <50%, and there is a growing recognition of its potential to worsen neurodevelopmental outcome.

Levetiracetam is a drug with a different mechanism of action and has been used in children and adults with good efficacy and safety. It is thought to act through interaction with the synaptic vesicle protein 2A, which is implicated in the control of synaptic vesicle fusion, exocytosis, and neurotransmitter release. Multiple studies reported the efficacy and tolerability of levetiracetam in acute seizure management, both as adjunctive and monotherapy in children.

Levetiracetam is also reported to be effective for the treatment of status epilepticus, nonconvulsive status, refractory status epilepticus, and electrical status epilepticus during sleep in children. Levetiracetam is increasingly being used to treat seizures in neonates. In a study with six newborns (body weight >2000 g and gestational age >30 weeks), levetiracetam was administered orally, and all six patients became seizure free within 6 days. Four of these patients received single phenobarbital doses before and during titration. Mild sedation was reported in one infant. Five patients remained seizure free after 3 months with ongoing levetiracetam monotherapy, and one infant developed pharmacoresistant epilepsy. In a study with 22 term neonates, levetiracetam was reported to stop seizures immediately in 86% and in all patients at the end of 72 h. Loading dose of levetiracetam was 10–50 mg/kg and maintenance dose was 25 mg/kg. Three patients (14%) were started on levetiracetam initially, and others were using other antiepileptic drugs, mostly phenobarbital. No serious side effects were reported.

Rakshashbuvankar et al. showed seizure cessation or at least 80% reduction of seizures in 6 of the 8 neonates with refractory seizures. Levetiracetam was administered as first-line treatment in 38 newborns in a study by Ramantani et al. They started levetiracetam at 10 mg/kg, increased to 30 mg/kg over 3 days, and titrated up to 45–60 mg/kg. They reported that 30 infants were seizure free under levetiracetam at the end of the 1st week and 27 remained seizure free at 4 weeks. EEGs markedly improved in 24 patients in 4 weeks. In a cohort of 23 neonates, levetiracetam was associated with a greater than 50% seizure reduction in 35% (8 of 23) of the neonates, including seizure termination in seven patients. The mean initial dose of levetiracetam was 16 ± 6 mg/kg, and the mean maximum dose was 45 ± 19 mg/kg/day. It was administered as a first-line anti-seizure medication in 4 neonates (17%), second-line in 14 neonates (61%), and third-line or later in 5 neonates (22%). In a retrospective chart review of three infants aged between 2 days and 3 months, who were initially treated with other antiepileptic drugs, each patient was reported to be seizure free on levetiracetam without adverse effects. Levetiracetam was reported to be effective in controlling both ictal and interictal status in a neonate with malignant migrating partial seizures unresponsive to phenytoin, phenobarbital, midazolam, vigabatrin, lamotrigine, clonazepam, and pyridoxine. Levetiracetam was reported to be effective in controlling status epilepticus in a neonate with Sturge–Weber syndrome. In a retrospective study of 127 neonates ≥36 weeks gestation with hypoxic–ischemic encephalopathy, 32 received levetiracetam after phenobarbital, and the seizures
stopped in 27 of these neonates.[18] A systematic review of the efficacy of levetiracetam in neonatal seizures suggests that levetiracetam may be at least or more effective for neonatal seizures as phenobarbital.[19]

Studies about levetiracetam use in preterm neonates are limited. Retrospective analysis of 12 preterm infants by Khan et al.[13] showed 82% seizure cessation within the first 24 h of levetiracetam in preterm neonates without serious side effects. Patients received a loading dose of 25 and 50 mg/kg. Maintenance dose was 25 mg/kg. Three (25%) patients were initially started on levetiracetam, others were priorly receiving phenobarbital. A retrospective analysis of 37 preterm infants reported that 21 infants (57%) were seizure free with levetiracetam as the first-line treatment at the end of the 1st week.[19]

In our study, we evaluated the efficacy and safety of levetiracetam in preterm and term neonates. Levetiracetam, as a second-line agent after phenobarbital, controlled seizures in 69.4% of the patients, and EEGs improved in 77.8% of the patients. Levetiracetam controlled seizures in 76.5% (13/17) of neonates <28 weeks and 63.6% (7/11) of neonates between 28 and 36 weeks, and 62.5% (5/8) of term neonates. This study suggests that intravenous levetiracetam can be a therapeutic option for seizure management in preterm and term neonates.

Levetiracetam is known as neuroprotective. In a study comparing neurotoxic properties of sulthiame and levetiracetam on developing rat brain, it was reported that sulthiame significantly enhanced neuronal death in the brains of rats but levetiracetam did not show this neurotoxic effect.[21] Another study showed that systemic hypoxia differentially affected expression of hypoxia-inducible transcription factor-1 (HIF-1)-regulated vasoactive factors in the newborn mouse brain, and levetiracetam treatment did not alter HIF-1-regulated neuroprotective mechanisms.[22] In the rat middle cerebral artery occlusion model, levetiracetam reduced the infarct volume suggesting neuroprotective properties.[23] Maitre et al.[27] reported worse Bayley Scales of Infant Development cognitive and motor scores with increased exposure to phenobarbital, and the effect was less with levetiracetam in 280 infants with comparable seizure etiology and cranial imaging results. Rats with hypoxic–ischemic brain injury were treated with levetiracetam, and the number of apoptotic brain cells decreased.[40] Neuroprotective effects of an antiepileptic drug might be particularly important during the neonatal period. On the basis of these findings, levetiracetam may be an especially good candidate for the treatment of seizures in neonates.

Pharmacokinetic studies have established a benign safety profile for levetiracetam.[24] Levetiracetam is not expected to cause significant drug interactions as it is less than 10% protein bound in plasma, and it is not dependent on liver cytochrome P450 enzymes for metabolism.[24] In a study about the pharmacokinetics of levetiracetam in neonates, it was observed that neonates had lower clearance, higher volume of distribution, and a longer half-life than children and adults.[16] The study consisted of 18 neonates ≤30 days of age and ≥32 weeks gestational age. Mild somnolence was the only reported effect.[16] A review on pharmacokinetics of levetiracetam in neonates reported no significant interactions with other drugs and no severe side effects, as it is not bound to plasma proteins.[41]

Studies about levetiracetam use in neonates did not report serious side effects except mild sedation in some infants.[14,16,17] A neonate has been reported to develop anaphylactic shock due to intravenous administration of levetiracetam.[42] In our study, levetiracetam was tolerated well, and no important side effects were evident. Only two patients (5.5%) had cytopenia during maintenance treatment. But this could not be clearly attributed to levetiracetam as the patients were also receiving phenobarbital. Levetiracetam can cause neutropenia. However, this has not been mentioned before in other reports about levetiracetam use in neonates. White blood cell counts of the patients increased after levetiracetam and phenobarbital were discontinued. The major limitation of our study was the lack of continuous EEG monitoring of the patients during the treatment.

In conclusion, our data suggest that levetiracetam may be a safe and effective treatment for neonatal seizures, which are unresponsive to phenobarbital. Larger, randomized controlled trials should be performed to assess the efficacy and safety for levetiracetam in neonates.

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Conflicts of interest
There are no conflicts of interest.

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