Levetiracetam – An Alternative Option in Preterm Neonates for Acute Seizure Management

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Neonatal seizures occur in five of 1000 live births in North America and affect the future development of the child. Preterm neonates are more susceptible to seizures due to brain immaturity with the incidence of 11 of 1000 live births, much higher than neonatal seizures. Few medicines studied and approved to treat this subset of patients, management difficult. The only medicines approved by the FDA are phenytoin and Phenobarbital in the neonatal period. Failure of these agents due to lack of efficacy and undesirable side-effects led us to investigate the role of Intravenous Levetiracetam in preterm neonates, the most challenging group of patients in the pediatric population. In this research highlight, we will discuss the findings of our recent in preterm neonates.

Keywords: Preterm neonates; Intravenous Levetiracetam; Seizures; Video-EEG monitoring


Neonatal seizures have deleterious effects on the developing brain, so their prompt recognition and treatment is crucial to prevent future adverse effects. The most common causes of seizures in the neonatal period are hypoxic–ischemic encephalopathy, central nervous system infections, infarctions, hemorrhages and metabolic abnormalities. The incidence of seizures in the neonatal period is five out of 1000 live births, and in the preterm neonates are 11 out of 1000 live births. The only medicines approved by Federal Drug and Food Administration are phenobarbital and phenytoin. Literature search reveals that phenobarbital is still the most commonly used medicine in this age group despite evidence of neuronal apoptosis in animal models and long-term neurodevelopment side-effects. In contrast to phenobarbital, there has been evidence that levetiracetam has neuroprotective properties, which may prove beneficial during the neonatal period because of rapid brain growth and physiological maturation of synapses during this period. Kilicdag and colleagues studied a levetiracetam treated group of rat pups who underwent a hypoxic–ischemic brain injury. Their results showed a significant decrease in the number of apoptotic neuronal cells suggestive of neuroprotective properties of levetiracetam.

Several studies have shown efficacy of Levetiracetam in neonates and children over the last few years. These also include our previous studies in older children and neonates. In our first study, we conducted a retrospective review of patients from 2months to 18 years of age. Data were acquired from electronic medical records for patients admitted for acute seizure management in the hospital between August 2006 and
May 2008. The loading dose used was 25–50 mg/kg. Our data analysis showed a favorable response to intravenous levetiracetam for all patients; and seizures were aborted both clinically and electrographically \(^\text{[22]}\). This led us to conduct a second study in the neonatal population. We retrospectively reviewed electronic medical records of neonates treated for neonatal seizures with intravenous levetiracetam between January 2007 and December 2009. We identified 22 neonates who received intravenous levetiracetam with the loading doses ranging between 10 to 50 mg/kg. The etiologies for neonatal seizures in our patient group included hypoxic–ischemic encephalopathy, intracerebral hemorrhage, viral meningoencephalitis, brain malformation, trauma, benign neonatal seizures, cryptogenic partial seizures and glucose 1 transporter deficiency. Seizure cessation was achieved in 86% (19/22) of patients one hour after the loading dose. One hundred percent seizure cessation was achieved by 72 hours after the loading dose. No serious adverse effects were noted and the conclusion was intravenous levetiracetam can be used in this age group \(^\text{[23]}\).

Our recent study researched the role of intravenous levetiracetam in preterm neonatal seizures. This was also a retrospective study that analyzed the electronic medical records of the infants, who were born less than 37 weeks of gestational age and received a dose of the anticonvulsant during the neonatal period. Our institutional review board approved the study. The duration of the data collection was from January 2007 to December 2011. The main objective of the study was to analyze the seizure cessation at 24 hours after the loading dose based on clinical data and EEG documentation. The other objective was to assess the time when complete seizure cessation occurred while on a maintenance dose. We also collected data about indications of the use of levetiracetam, the side effects and clinical outcomes in terms of seizure control at the well-child visits.

Our data included 12 preterm neonates, which fulfilled the inclusion criteria. There were eight females (67%) and four males (33%). These include five Caucasians, five Hispanics, and two African Americans. The gestational ages ranged from 23.3 to 36 weeks and birth weights between 0.62 to 2.96 kg. The range of Apgar scores at one minute ranged between 0 and 9. The most common etiology was hypoxic ischemic encephalopathy seen in five of the patients, followed by hemorrhages in three, unknown seizure etiology in three, and one with herpes simplex virus encephalitis. The diagnostic techniques utilized included imaging data and continuous video EEG monitoring. The loading dose of 50 mg/kg was given to seven patients with maintenance dose of 25 mg/kg every 12 hours. The loading and maintenance dose of 25 mg/kg was given to five patients. The main indication for the use of levetiracetam was continuation of seizures despite management with phenobarbital in 9/11 (75%) of these patients. Three patients were started on levetiracetam as first line. Six patients remained on a combination of phenobarbital and levetiracetam. The response to treatment was based on clinical data and the results of continuous video EEG monitoring. The results showed that 9 out of 11 patients had seizure documentation by 24 hours of the loading dose and 10 patients achieved seizure cessation by 72 hours as determined by continuous video electroencephalogram (EEG) correlate. No immediate side effects were noted. Eleven of our patients, who received intravenous levetiracetam, were followed at 6 months at a well-child clinic. Of these, six patients were seizure free and were weaned off medication and three remained seizure free on oral medicine. This study seems to be the first to focus on preterm neonates and concludes that intravenous levetiracetam appears to be safe in acute seizure management of preterm neonates. The limitations of our study are retrospective design and small sample size \(^\text{[24]}\).

Our group is recently involved in a seven-year retrospective review of the role of intravenous levetiracetam in acute seizure management. However, there is a pressing need for further, larger, prospective multicenter trials clarifying the role of this anticonvulsant in this pediatric subgroup.

**Conflict of interest**

The author declares that they have no conflict of interest.

**References**


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