Levetiracetam in Neonatal Seizures as First-line Treatment: A Prospective Study

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INTRODUCTION

Neonatal seizures include those critical events whose onset has occurred during the first 28 days of life and till date, phenobarbital and phenytoin remain the most common anticonvulsive drugs administered in this age group. When administered apart, these drugs result in resolution of <50% of neonatal seizures.[1] When used in combination, the percentage of seizure resolution rises up to 60% of all treated cases.[2]

Considering that etiology and presentation of neonatal seizures are different from the children and adult ones, the most recently proposed International League Against Epilepsy classification suggested that neonatal seizures should not be considered as distinct types, but could be classified within its general and universal scheme as focal seizures and others, as others including subtle seizures, clonic seizures, myoclonic seizures, and tonic episodes.[3]

Aim of the Study: The aim of this study is to evaluate the efficacy and safety of levetiracetam (LEV) as first-line treatment of neonatal seizures.

Materials and Methods: This study was conducted in patients of Neonatal Intensive Care Unit of Santo Bambino Hospital, University of Catania, Italy, from January to August 2016. A total of 16 neonates with convulsions not associated with major syndromes, which required anticonvulsant therapy, were included and underwent IV LEV at standard doses. Results: All patients responded to treatment, with a variety range of seizure resolution period (from 24 h to 15 days; mean hours: 96 ± 110.95). No patient required a second anticonvulsant therapy. Regarding safety of LEV, no major side-effects were observed. Conclusions: To our knowledge, it is one of the few studies confirming the efficiency of LEV as first-line treatment in seizures of this age group. LEV was effective in resolving seizures and was safely administered in the current study.

KEYWORDS: Efficiency and safety, levetiracetam, neonatal seizures, prospective study

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Acute side effects of phenobarbital and phenytoin include hypotension, respiratory suppression, cardiac arrhythmias, and sedation. Chronic administration of phenobarbital seems to be associated with long-term impairment of neurological development and secondary decrement of cognitive abilities.[4,5] The use of these drugs, although widely administered in Neonatal Intensive Care Units (NICUs), is not until now supported by studies suggesting their higher efficiency with respect to other anticonvulsant drugs of the last generation. In regards, in 2013, Maitre et al. showed a safer profile of levetiracetam (LEV) than phenobarbital, with less side effects on cognitive development in the LEV-treated subjects.[5] Moreover, studies on animal models suggested...
that phenobarbital and phenytoin seem to have an effect of acceleration of the neuronal apoptosis, above all when administered to premature babies. On the contrary, LEV has been described as having a good tolerability profile and efficiency in the resolution of pediatric seizures. Actually, the molecule has been approved as add-on therapy for the treatment of focal seizures in patients over 4 years of age in Europe and over 1 month of life in the United States. Moreover, in 2013, LEV was approved as first-line treatment in some epilepsies of adulthood, and benign epilepsy of children with centrotemporal spikes.

The molecule safety was confirmed by in vivo studies of animal models, reporting no neurotoxic side effects at therapeutic doses. Furthermore, the molecule was shown to be effective in diminishing seizures secondary to the hypoxic-ischemic syndrome, in addition to successful prognosis improvement. It appears that LEV has an anti-apoptotic effect, which eventuates in the reduction of cellular apoptotic processes in the hippocampus and cerebral cortex of treated patients.

To our knowledge, there are poor literature data on the use of LEV in NICU as an anticonvulsant drug for neonatal seizures, and little is known on its efficiency as first-line treatment in this age group.

The aim of this study was to evaluate the efficacy and safety of LEV as first-line treatment of neonatal seizures, using a therapeutic protocol with LEV alone at onset, and eventual phenobarbital as adjunctive therapy in those LEV-resistant convulsive forms.

**Materials and Methods**

We performed a prospective observational study on preterm and on-term infants, affected by neonatal seizures, requiring anticonvulsant treatment. Patients were recruited from July 2015 to July 2016, in the NICU of the Santo Bambino Hospital of Catania, Policlinico-Vittorio Emanuele University Hospital, University of Catania, Italy.

We randomly included all preterm and born-on-term neonates with signs and/or symptoms of the convulsive disease and/or hypoxic-ischemic disease, both with continuous video-electroencephalogram (EEG) correspondent pathologic results and without electrophysiological signs, not associated with known major neurologic diseases, who needed anticonvulsant therapy according to their neurologic clinical condition.

All patients with known major neurologic diseases and/or syndromes, with neurologic symptoms due to metabolic causes (e.g., tremors from hypocalcemia and/or hypoglycemia), with major cardiovascular and surgery diseases, and/or with known hypersensitivity to the drug, were excluded from the study. All included patients underwent a therapy with IV LEV at standard doses (initially, 10 mg/kg twice daily, with gradually increasing doses up to 40 mg/kg twice daily in case of nonresponse to lower doses. The increase was performed every 24 h, of 10 mg/kg/pro dose in case of persistence of seizures). The study protocol also considered the use of phenobarbital as adjunctive therapy in those cases resistant to LEV.

All included patients performed clinical and diagnostic evaluation at baseline (T0) and after 3 months (T1) and 6 months (T2) from the beginning of therapy, to study efficiency and safety of the protocol study.

At baseline, the following data were collected: Patients’ demographic data, familial and personal historical records, signs and/or symptoms description, inclusion and exclusion criteria evaluation, blood routine tests, cerebral ultrasound scan, electroencephalogram, and neuroimaging (computed tomography scan, cerebral magnetic resonance imaging [MRI]) in those required cases.

To evaluate the efficiency of LEV, we collected the following data at T1 and T2: clinical progression, time of seizures resolution, inter- and intra-critical continuous video-EEG, and cerebral ultrasound scan progression. The safety was evaluated by the presence of side effects and blood routine tests with evaluation of renal and kidney functions.

Informed consent was obtained from all patients’ parents before the onset of therapy.

The study protocol conformed to the ethical guidelines of the 1975 Declaration of Helsinki as revised in 2000 and was approved by the ethic committee of our institutions.

**Statistical analysis**

For statistical evaluation, we used dedicated software: JMP (product of SAS Institute Inc., Cary, NC 27513-2414, USA) and GraphPad 5.0 (La Jolla, CA, USA.). We expressed the qualitative variables as percent and the quantitative as mean ± standard deviation (SD). For the data expressed as mean ± SD, we tested the approximation to normal of the distribution of the population by Kolmogorov–Smirnov One-Sample Test and statistics for kurtosis and symmetry.

**Results**

The sample population included 16 neonates, of whom 12 were born on term, whereas 4 were preterm (2 were born at 35th, and 2 at 36th gestational weeks). Mean weight of...
patients was estimated 2690.55 g (SD: ±1101.63). The mean head circumference was 34.31 ± 1.90 SD.

Among included patients, 12 (75%) were born by cesarean section and 4 by vaginal delivery. In general, positive perinatal history of the sample included meconium aspiration syndrome (31.2% of cases), respiratory distress (50%), fetal blood circulation disease (12.5%), and acute placental detachment (18.75%). Mean Apgar index at 1st min was 5.12 (±3.70 SD), and 6.87 (±3.20 SD) at 5th min. All included neonates showed generalized hypotonia (both axial and peripheral) at birth. Mean onset of symptoms was 3.3 ± 1.2 days and symptoms for which LEV was started included ocular involvement (12.5%), focal seizures (12.5%), generalized tremors (50%), and tonic-clonic seizures (12.5%) [Figure 1].

EEG study before treatment showed the presence of brushes in 12.5% of patients, diffuse cortical involvement in 12.5% of cases and centrottemporal spikes in 12.5% of patients [Figure 2].

Cerebral ultrasound scan before treatment was normal in 12 cases (75%), showed a thinning of the corpus callosum in two cases (12.5%), Grade I intraventricular hemorrhage in two cases (12.5%) and choroid plexus hemorrhage in two cases (12.5%).

MRI was performed in 40% of cases for neurological signs associated, and it was almost normal, except of one case that showed the presence of thalamic porencephaly.

After 3 months of treatment, all pathologic EEGs were normal when referred to gestational age. As far as cerebral ultrasound scan, in those cases highlighting the presence of hemorrhage, this was reabsorbed at T2.

All patients responded to treatment, with a variety range of seizure resolution period (from 24 h to 15 days; mean hours: 96 ± 110.95) [Figure 3]. No patients required a second anticonvulsant therapy. Regarding safety of LEV, no major side effects were observed. Nearly 50% of the cases presented lethargy and feeding difficulty, which were resolved after reduction adjustments of the drug doses. Routine blood tests were normal in 87.5% of cases, whereas in two cases (12.5%), we observed a slight hypertransaminasemia, which were resolved after adjustments of LEV doses.

**DISCUSSION**

In this study, we found that LEV alone was efficient and safe in the resolution of neonatal seizures. To our knowledge in literature, there are really few data on the use of LEV as first-line treatment in seizures of this age group and in preterm neonates. As a matter of fact, there are poor literature data on the use of this molecule in neonates, differently of what reported in pediatric age.

The first published data on the use of LEV in neonates dates back to 2011 when Khan et al. reported isolated cases, studying its IV use as second-line treatment of acute neonatal seizures, following a first-line step with phenobarbital, which was ineffective.[10] In the same year, Abend et al.[11] led a retrospective study on 23 on-term neonates affected by neonatal seizures with pathologic EEG, of probable hypoxic-ischemic origin.
In this study, LEV was initiated at a mean conceptional age of 41 weeks. All patients received an initial dose of 10/20 mg/kg of LEV, with a subsequent maintenance dose of 45 ± 19 mg/kg/die. Seizures onset was observed in a mean of 3.3 ± 1.2 days, according to literature data reporting a longer latency of seizure onset in neonates under 29 weeks of gestation (mean 8.3 days of life) compared to newborns with higher gestational age, between 30 and 36 weeks (mean 3.2 days of life). This is probably according to the immature synapse structure and myelinization in children under 29 weeks of gestation. Seizures resolution was observed after 24 h of treatment in 8/23 neonates and between 24 and 72 h in other four patients; in other three patients, it was not possible to evaluate LEV efficiency, as the treatment was started after seizures resolution. The remaining 8 patients did not respond to LEV.

Later, Ramantani et al. published a study on the use of LEV as first-line treatment in 38 on term and preterm neonates; the drug was administered IV at initial dose of 10 mg/kg/dose, with a gradual daily increase up to 30 mg/kg/die, and in case of persistent seizures up to 45/60 mg/kg/die. In case of drug resistance to LEV alone or associated with pyridoxine, phenobarbital was added. In this study, LEV was safely administered both to on term and preterm babies, although, when administered alone, was not efficient in solving seizures, and phenobarbital was added in more than 50% of the studied patients.

Recently, in 2013, Maitre et al. published a retrospective study to evaluate the neurodevelopmental progression of 280 neonates treated with phenobarbital and LEV. The authors confirmed the same results already found in animals, thus an increased neurotoxicity and altered neuromotor development in phenobarbital-treated patients. On the contrary, they demonstrated a reduction of neuronal apoptosis and a better neuromotor outcome in the LEV-treated group. Nevertheless, in this study, LEV was used as adjunctive therapy, on a second-line choice.

Finally, in 2015, Yau et al. published a retrospective study on 6 neonates treated with LEV within the first 4 weeks of life, having a control of seizures in about 75% of treated cases and within 72 h from the onset of treatment. No side effects were observed, although all patients received a first dose of phenobarbital before being treated with LEV.

Literature data on the use of LEV in NICU are poor and contradicting, even if all these studies are limited in number of included patients and poorly descriptive in methods for the evaluation of efficacy.

In this study, we analyzed the efficiency of LEV not only on a clinical point of view but also on an electrophysiological basis, by video-EEG and on a neuroimaging basis, by cerebral ultrasound scan.

In this study, we found a resolution of seizures in all treated patients, with no needing for an adjunctive anticonvulsant therapy. This clinical improving was also associated with an electrophysiological improvement after 3 months of treatment and to an equivalent ultrasound scan improvement after 6 months of therapy. This in line with the anti-apoptotic effect of LEV. In regards, several studies have suggested a neuroprotective effect of LEV in both epileptic and nonepileptic disorders. LEV has been demonstrated to increase the expression of gamma glutamate transporters (GLTs) excitatory amino acid transporter 1/glutamate–aspartate transporter (EAAT1/GLAST) and EAAT2/GLT1, which mechanism has been proposed one of the most important effects of LEV in neuroprotection. This hypothesis fits well with those changes described in brains after traumatic insults, consisting in increased concentration of glutamate in the extracellular areas, with secondary enhanced activation of N-methyl-D-aspartate receptors and alpha-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptors on neurons and culminating in neurodegeneration. In this context, LEV has also been demonstrated to decrease the expression of pro-oxidant protein-inducible nitric oxide synthase and increase the expression of the antioxidant protein cysteine/glutamate exchanger in the hippocampus, diminishing those damages caused by seizure-induced oxidative stress.

Regarding safety of LEV, no major side effects were observed. Only minor effects were observed (50% of the cases presented lethargy and feeding difficulty, and in two cases a slight hypertransaminasemia was observed) all resolved after adjustments of LEV doses.

Although the present scientific literature supports the use of LEV in neonatal seizures, further protocols and studies need to reinforce this advice, with protocol guidelines in this age group, also drafting multicenter, randomized, placebo-controlled studies involving a higher number of neonates in treatment and comparing the efficiency of LEV as first-line treatment with other anticonvulsant drugs.

**Conclusions**

To our knowledge, it is one of the few papers on the use of LEV as first-line treatment in seizures of this age group and above all the second study using LEV in preterm neonates. LEV was efficient in resolving
seizures and was safely administered in the current study, a finding which is consistent with present literature data. Nevertheless, the majority of studies mostly consider LEV as a second-line treatment, after standard therapy with phenobarbital is failed in seizures resolution. In this study, LEV was independently efficient in treating neonatal seizures, while significantly decreasing the risk probability for adverse events (which are usually associated with phenobarbital). Therefore, we reinforce our suggestion for the draft of multicenter clinical trials to design guidelines on the use of LEV in neonatal seizures.

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Conflicts of interest

There are no conflicts of interest.

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