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Evaluation of the efficacy and safety of levetiracetam treatment for neonatal seizures in extremely preterm infants

İleri derece preterm bebeklerde neonatal nöbetler için levetirasetam tedavisinin etkinliğinin ve güvenilirliğinin değerlendirilmesi

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Abstract

Aim: Levetiracetam (LEV) is increasingly being used to treat seizures in the neonatal period. Data about using LEV in extremely preterm infants with seizures is insufficient and limited with only a handful studies. This study aimed to evaluate the efficacy and safety of LEV in the treatment of seizures in extremely preterm infants.

Methods: This retrospective cohort study was conducted on extremely premature newborns, those who were born ≤28 weeks of gestational age, and took their first intravenous dose of levetiracetam due to neonatal seizure before their 44th gestational week between September 2017-February 2019. Loading and maintenance dosage of LEV, previously used antiepileptic medications, response to treatment and side effects of LEV were recorded.

Results: Twenty extremely preterm neonates (9 males and 11 females) who received LEV were evaluated. Gestational ages ranged from 23 to 28 weeks, with a median of 26.5 weeks. Birth weights ranged from 520-1210 gr and 15 infants (75%) had extremely low birth weights. For the treatment of seizures, 12 patients (60 %) were initially started on levetiracetam as first-line therapy and eight patients (40%) were administered levetiracetam as a second or third-line antiepileptic drug. The efficiency of seizure control with LEV was 60 % (12/20) in all patients. The median LEV dose at the time seizure control was achieved was 40 mg/kg. No side effects were observed due to LEV treatment.

Conclusion: This study shows that LEV can be efficient and safe for seizure management in extremely preterm infants. Seizure control was better achieved when LEV was given as the first-line antiepileptic medication in extremely preterm infants.

Keywords: Levetiracetam, Neonatal seizures, Preterm

Öz

Amaç: Levetirasetam (LEV), yenidoğan döneminde nöbetleri tedavi etmek için giderek daha fazla kullanılmaktadır. Nöbet geçiren ileri derece preterm bebeklerde LEV kullanımı ile ilgili veriler yetersizdir ve sadece birkaç çalışma ile sınırlıdır. Bu çalışma, ileri derece preterm bebeklerde nöbetlerin tedavisinde LEV'in etkinliğini ve güvenilirliğini değerlendirmeyi amaçlamıştır.

Yöntemler: Bu retrospektif kohort çalışma, Eylül 2017-Şubat 2019 tarihleri arasında ≤28. haftalık gebelik haftasında doğan ve yenidoğan nöbeti nedeniyle ilk doz intravenöz levetirasetamı postnatal 44. haftaya kadar alan ileri derece preterm yenidoğanlarda yapılmıştır. LEV'in yükleme ve idame dozu, daha önce kullanılan antiepileptik ilaçları, tedaviye yanıtı ve LEV'in yan etkileri kaydedildi.

Bulgular: Levetirasetam alan 20 ileri derece preterm yenidoğan (9 erkek ve 11 kadın) değerlendirildi. Gestasyonel yaşları 23 ila 28 hafta arasında değişiyordu ve ortalama 26.5 hafta idi. Doğum ağırlıkları 520-1210 gr arasında değişiyordu 15 bebek (%75) aşırı düşük doğum ağırlıklıydı. Nöbetlerin tedavisi için başlangıçta birinci basamak tedavi olarak 12 hastaya (%60) levetirasetam başlandı ve sekiz hastaya (%40) ikinci veya üçüncü basamak antiepileptik ilaç olarak levetirasetam verildi. Tüm hastalarda LEV ile nöbet kontrolünün etkinlik oranı %60 (12/20) idi. Nöbet kontrolü sağlandığında ortalama LEV dozu 40 mg/kg olarak bulundu. LEV tedavisine bağlı herhangi bir yan etki gözlenmedi.

Sonuç: Bu çalışma, LEV'in ileri derece preterm bebeklerde nöbet yönetimi için etkili ve güvenli olabileceğini göstermektedir. İleri derecede preterm bebeklerde LEV birinci basamak antiepileptik ilaç olarak verildiğinde nöbet kontrolü daha iyi sağlanmıştır.

Anahtar kelimeler: Levetirasetam, Neonatal nöbetler, Preterm

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Introduction

Seizures are one of the most common and serious neurological emergencies in the neonatal period [1,2]. Neonatal seizures occur in 1-3 per 1000 term newborns and it may increase up to 10-130 per 1000 in preterm neonates [2-4]. The neonatal period is the most important period of life for developing seizures, because neonatal seizures, especially if prolonged, were reportedly associated with poor neurodevelopmental outcomes, as it may negatively affect the immature brain of premature infants [1,5,6]. Therefore, treatment and management of neonatal seizures are particularly important to reduce neurological disabilities of children [1,5].

Neonatal seizures usually manifest with stereotypical muscular activity or autonomic changes, and are a result of abnormal electrical discharges in the central nervous system of neonates, occurring within the first 28 days after birth in full-term infants or until 44 weeks of gestational age in preterm infants [1,4,7]. The etiologies of neonatal seizures are reported in a broad spectrum, such as hypoxic-ischemic encephalopathy (HIE), infections, metabolic and electrolyte disturbances, brain injuries, intraventricular hemorrhage (IVH), periventricular leukomalacia (PVL) and brain malformations [1,8]. Extremely preterm infants who are born ≤28 weeks gestational age may be more vulnerable to neonatal seizures than other preterm and term neonates due to the immaturity of their nervous system, and they can have a lot of comorbidities including various disorders of the brain, which may lead to the decrease of seizure threshold [7,9].

Despite a highly broad spectrum of etiologies and their importance on neurodevelopmental outcomes, we only have a few treatment options to manage neonatal seizures. In the neonatal period, phenobarbital and phenytoin are well known and the most often used antiepileptic drugs, because they are the only two drugs which have been approved by the FDA for the treatment of neonatal seizures [1-3]. However clinical studies showed that both have some side effects during the acute seizure treatment period or long-term use [2,5,10]. The use of phenobarbital may have a negative effect on long-term neurodevelopmental outcomes [2,10] . Similarly, long-term use of phenytoin in newborns is associated with some serious potential side effects such as arrhythmia, hypotension, and serious tissue necrosis if extravasated during administration [10]. On the other hand, the efficacy of phenobarbital and phenytoin in controlling neonatal seizures is around only 75-85 %, even when used together [1,11]. In addition, the intravenous form of phenobarbital to treat acute seizures cannot be found in our country. During the last decade, treatment preferences in lots of countries for neonates with seizures have begun to change towards other anti-seizure medication drugs, especially LEV.

Animal studies demonstrated that LEV may reduce apoptosis on the neonatal brain and may lead to neuroprotection, and clinical studies show that LEV is related to good neurodevelopmental outcomes of neonates with seizures [2,12]. Even though the use of LEV in neonates has not been approved by FDA yet, in the literature, studies which evaluate the use of LEV in neonatal seizures have increased in the last decade [2,13,14]. These clinical studies showed that LEV can be used to control seizures in term neonates safely and effectively [2,13]. However, data about efficacy and safety of using LEV in even preterm infants is limited, data about using LEV in extremely preterm infants with seizures is even more insufficient and is limited to only a handful studies [4,9,15]. This study aims to evaluate the efficacy and safety of LEV in the treatment of seizures in extremely preterm infants.

Materials and methods

Study population

We performed a retrospective cohort study in the neonatal intensive care unit at Adana City Training and Education Hospital, Adana/Turkey from September 2017 to February 2019. Extremely preterm newborns who were born ≤ 28 weeks of gestational age and took their first intravenous levetiracetam due to neonatal seizures until the 44th gestational week were included in the study. Infants whose seizures were caused by electrolyte disturbances or metabolic (i.e., hyponatremia, hypocalcemia, hypomagnesemia, or hypoglycemia) reasons, those who had pyridoxine-responsive seizures and all infants born later than the 28th gestational week were excluded. This study was approved by the institutional review board Ethics Committee of Çukurova University Medicine Faculty, Adana, Turkey (2019/89).

Data collection

Data was collected by a medical record review of detailed prenatal and postnatal variables of babies and mothers including maternal parity, consanguinity of parents, familial history, maternal age, type of delivery, gestational age, birth weight and gender. Perinatal disorders usually associated with premature labor were also recorded. Based on gestational age, our sample was divided into 2 subgroups: 1) <27 weeks and 2) 27-28 weeks. Small for gestational age (SGA) was defined as birth weight <10th percentile on Fenton growth curves. Birth weight less than 1000 gr was accepted as extremely low birth weight.

Apgar scores at the 1st and 5th min were recorded and whether the baby was resuscitated at birth was evaluated. Apgar scores were ranked as follows: Below or equal to three, between four and seven, and equal to or above eight. Physical and neurological examination findings of babies were noted. Detailed laboratory parameters (including complete blood count and serum sodium, glucose, blood urea nitrogen (BUN), creatinine, potassium, chlorine, calcium, serum aspartate aminotransferase (AST), serum alanine aminotransferase (ALT), arterial blood gas, total bilirubin, C-reactive protein (CRP)) were obtained from all patients**.**

Seizure protocol

Neonatal seizures were diagnosed based on the clinical observation of doctors (neonatologists, pediatricians, and pediatric neurologists) and nurses, and findings of neurological and physical examinations. Types of seizures were defined according to Volpe's classification, including subtle, tonic, clonic and myoclonic seizures, by a pediatric neurologist. The time of seizure onset was classified as occurring within the first 24 h, between 24 to 72 h, between 3 and 7 days, and over 7 days after birth. Seizure etiologies were evaluated.

Loading and maintenance dosage of LEV, previously used anti-seizure medications, concomitant treatments with other

AEDs, response to treatment, side effects during or after the loading or maintenance dosage of levetiracetam were recorded. The use of LEV as first, second- and third-line anti-seizure medication were evaluated.

At our institute, phenytoin, midazolam, and LEV are administered intravenously, but PB is given orally at our NICU because the intravenous form of PB is absent in our country. LEV is mixed with normal saline and initially loaded intravenously (IV) over one hour. Loading and maintenance dosage of levetiracetam were determined by pediatric neurologists on a case-by-case basis. The maintenance dosage of LEV after loading is administered twice daily. The anti-seizure medications were considered effective when the seizure terminated within one hour after LEV administration and did not recur for at least 24 h.

Anti-seizure medications were considered safe and tolerable if patients showed no changes in vital signs, clinical-laboratory parameters, or electrocardiography abnormalities during the treatment period. Length of hospital stay, presence of any comorbidities and complications (intraventricular hemorrhage, PVL, hydrocephalus with or without a ventriculoperitoneal shunt, etc.) and mortality rate were evaluated.

Statistical analysis

Statistical analyses were performed using SPSS version 16.0 (SPSS, Inc., Chicago, IL, USA). Qualitative and quantitative (continuous) variables were presented as the number of cases (n) with percentages (%), mean (standard deviation (SD)), median and range, respectively. Fisher's exact test was used for the evaluation of nominal variables according to the response to LEV treatment because of our small sample size. A value of P <0.05 was considered statistically significant.

Results

Within the study period, 928 infants were admitted to the NICU, 49 of which met the seizure criteria, and 29 neonates were excluded. A total of 20 neonates who were born before 28 weeks GA were included in the study (Figure 1).

We retrospectively analyzed 20 extremely preterm neonates (9 males and 11 females) who received LEV monotherapy, or a combination therapy including LEV. The median age of mothers was 26 years, and 20% of the mothers were primiparous. Eight (40%) patients were immigrants. According to the evaluation of pre-perinatal risk factors, ten patients had a least one risk factor while 4 patients had two and more. The most frequently seen prenatal risk factors were premature rupture of membranes (PROM) (n=9), and chorioamnionitis (n=4). The demographical and clinical features of the infants were shown in Table 1. Fifteen (75%) infants were delivered by C-section. Gestational ages ranged from 23 to 28 weeks, with a median of 26.5 weeks. Birth weights ranged from 520-1210 gr, with a median of 730 gr. Fifteen infants (75%) had extremely low birth weights (birth with less than 1000 gr) and two infants (10%) were SGA. Apgar scores at the 1st minute ranged from 2-7, with a median of 3.5, and Apgar scores at the 5th minute ranged from 5-9, with a median of 7. The 1st minute Apgar score was under 3 points in 10 patients and Apgar scores at the 5th minute were under 7 points in all patients except for four. Ninety percent of all patients were resuscitated at birth, and respiratory distress syndrome (RDS) was diagnosed in 16 (80%) neonates.

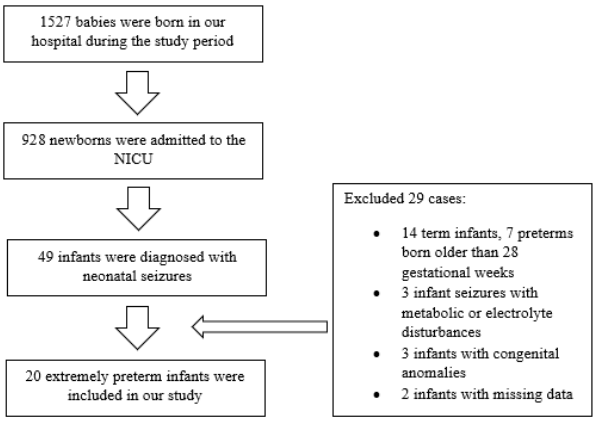

Figure 1: The flow diagram shows how patients were included in the study

The median of seizure onset was the 3rd day, and it varied between 2 and 26 days. The onset of seizure according to gestational ages ranged from 23 to 32 weeks. No patient had a seizure within the first 24 hours after the birth, 16 (80%) among all patients developed seizures within 7 days after birth (Table 2). Most patients presented with partial seizures with or without secondary generalization. The main seizure types were clonic (40%) and tonic seizures (25%), and five subjects (25%) presented with more than one type of seizures in different combinations (Table 2). Subtle type seizures were seen in six newborns (30%), majority of which were accompanied by clonic or tonic seizures. According to their etiologies of seizures, the most frequent diagnosis was germinal matrix hemorrhages (grade II to IV) which were seen in 12 (60%) of all infants.

Table 1: The characteristics of extremely premature infants (n=20)

Characteristics	Median	(Minimum - Maximum)
Gestational age (week)	26.5	23-28
Birth weight (g)	730	520-1210
Maternal age (year)	26.5	22-39
Maternal parity	3	1-5
Apgar 1st min	3.5	2-7
Apgar 5th min	5.5	5-9
Time of the seizure onset (day)	3.5	2-26
	n	Percentage
Gender (female) n, (%)	11	(65 %)
Cesarean section n, (%)	15	(75%)
Pre-perinatal complication n, (%)		
PROM	9	(45%)
Chorioamnionitis	4	(20%)
Preeclampsia	1	(5%)
Etiology of seizure n, (%)		
IVH	12	(60%)
Sepsis	4	(20%)
Meningoencephalitis	2	(10%)
HIE	2	(10%)
Accompanying comorbidities and complications		
RDS	16	(80 %)
PVL	6	(30%)
Hydrocephalus	4	(20%)
Mortality n, (%)	7	(35%)

PROM: Premature rupture of membranes, IVH: Intraventricular hemorrhage, HIE: Hypoxic-ischemic encephalopathy, RDS: Respiratory distress syndrome, PVL: Periventricular leukomalacia

For the treatment of seizures, 12 patients (60%) were initially started on levetiracetam as first-line therapy (Group 1). Group 2 consisted of eight patients, four of the which (20%) began receiving LEV as a second-line antiseizure drug because of continued seizures on phenytoin or phenobarbital, and four patients (20%) received LEV as third-line treatment because of continued seizures despite phenytoin and phenobarbital administrations (Table 2). The median first loading dose of LEV was 40 mg/kg (ranged; 20-45 mg/kg). Nine patients (45%) needed an additional loading dose to control the seizures, and the

maximum loading dosage of LEV was 70 mg/kg. The median LEV dose at the time when seizure control was achieved was 40 mg/kg (range: 20-70 mg/kg) and the median maintenance dose of LEV was 45 mg/kg/day (ranged; 20-60 mg/kg/day). The efficiency rate of seizure control with LEV was 60% (12/20) among all patients. The seizures were successfully managed in 67% (8/12) when LEV was used as the first-line drug and 50% (4/8) when LEV was used as the second or third-line drug (Figure 2). There were no statistically significant differences between the groups in terms of the rate of seizure management (P=0.64). When patients were evaluated according to favorable response to LEV treatment, we did not find any significant differences between the groups in terms of gestational age, birth weight, gender, delivery mode, Apgar scores, seizure onset, and loading dosage of LEV (P>0.05) (Table 3).

Table 2: Features of seizures and treatment of levetiracetam (n=20)

	Number of subjects	Percentage (%)
Time of seizure onset		
First 24 hours	-	-
24-72 hour	10	50
4-6 days	6	30
≥7 days	4	20
Seizure semiology		
Clonic	8	40
Tonic	5	25
Clonic - subtle	4	20
Tonic - subtle	1	5
Myoclonic	1	5
Subtle	1	5
Total	20	100
Treatment of levetiracetam		
First line	12	60
Second line	4	20
Third line	4	20
Seizure control rate with LEV	12	60
	Median	Range
Median first loading dosage of LEV	40 (mg/kg)	20-45 (mg/kg)
Median total loading dosage of LEV	40 (mg/kg)	20-70 (mg/kg)
Median maintenance dose of LEV	45 (mg/kg/day)	20-60 (mg/kg/day)
Side-adverse effects	-	-

Table 3: Characteristics of extremely preterm infants with favorable versus unfavorable response to levetiracetam

Values	Number of subjects (n, %)	Group 1 (n=12)	Group 2 (n=8)	P-value
Gestational age				0.65
23-26 week	10(50)	5	5	
27-28 week	10(50)	7	3	
Birth weight				0.69
<1000 g	15(75)	9	6	
>1000 g	5(25)	3	2	
Gender				0.19
Female	11(55)	5	6	
Male	9(45)	7	2	
Delivery mode				0.70
Cesarean	15(75)	9	6	
Spontaneous	5(25)	3	2	
Pre-perinatal complication				0.65
No	10	7	3	
Yes	10	5	5	
1-min Apgar score				0.65
0-3	10(50)	7	3	
4-7	10(50)	5	5	
8-10	0	0	0	
5-min Apgar score				0.53
0-3	0	0	0	
4-7	16(80)	10	6	
8-10	4(20)	2	2	
Seizure onset				0.69
<72hour		5	5	
≥72 hour		7	3	
Etiology				
IVH	12	7	5	
Sepsis	4	3	1	
Meningoencephalitis	2	1	1	
HIE	2	1	1	
Treatment of levetiracetam				0.648
First line	12(60)	8	4	
Second or third line	8(20)	4	4	
Median loading dosage of LEV, range (mg/kg)	40 (20-70)	40 (20-70)	40 (30-70)	
Exitus	7(35)	4	3	0.68

LEV: Levetiracetam, Group 1: Favorable response to LEV, Group 2: Unresponsive to LEV

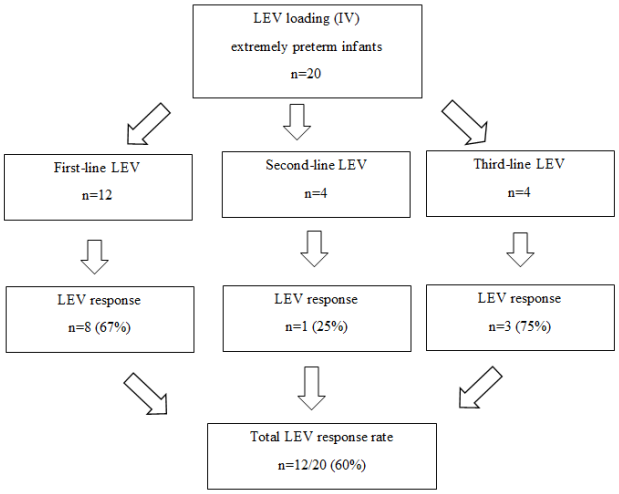

Figure 2: The efficiency rate of seizure control with LEV was 60 % (12/20) in all patients. The seizures were successfully managed in 67% (8/12) when LEV was used as the first-line drug and 50% (4/8) when LEV was used as the second-line or third-line drug (LEV: Levetiracetam)

No serious side effects were observed due to LEV infusion or oral administration in terms of clinical (changes of respiratory status, heart rate or blood pressure, somnolence, irritability, etc.) or laboratory (hepatic and renal dysfunction) parameters. The median length of hospital stay was 82 days (range; 7-142 day) and mortality rate was 35%.

Discussion

The present study conducted with 20 extremely premature neonates indicates that intravenous levetiracetam may be effective and safe in the management of acute seizures during the neonatal period. Seizure control was achieved in 60% of all patients, treatment with levetiracetam did not result in any adverse events and was generally well-tolerated in our study population.

Levetiracetam is a second-generation anticonvulsant with wide spectrum anti-seizure efficiency. In 2012, FDA approved the use of LEV in infants and children aged 1 month and older to treat focal seizures as an adjunctive antiepileptic medication. Animal studies demonstrated that LEV may reduce apoptosis on the neonatal brain and may lead to neuroprotection, and clinical studies show that LEV is related to good neurodevelopmental outcomes of neonates with seizures [12,13,16,17]. Although the use of levetiracetam in newborns has not been approved by the FDA yet, LEV has been increasingly used off label in neonates because of clinical reports in the literature showing efficiency and safety of using of levetiracetam in neonatal seizures, and animal studies showing the neuroprotective effects of levetiracetam [2,13]. The presence of side effects of phenobarbital and phenytoin during administration, the negative effects on long-term neurodevelopmental outcomes, and absence of intravenous form of phenobarbital in our country, the demonstration of the safety, well tolerability and neuroprotective effects of LEV led to a change of treatment preferences in neonates with seizures, in favor of LEV in our hospital as in the world.

Prematurely born infants, especially extremely premature infants, are more vulnerable to neonatal seizures than full-term infants [6,7,9]. They are born with a more immature central nervous system, most of the time they need longer intensive care and they may have lots of comorbidities which can

facilitate having a seizure [7]. Neonatal seizures should be monitored and treated carefully to avoid brain damage [1,5,7]. In premature babies, treatment of neonatal seizures quickly and choosing the drug with the least side effects at treatment and follow up are much more important than it is for full-term neonates in terms of long-term neurodevelopmental outcomes [7,9,15]. Also, the frequency of NEC is higher in prematures and they may not be able to take oral medicines for a long time. Therefore, the use of LEV, which has very few side effects in intravenous or oral use and is safe for a long-term treatment, may be a good option in premature cases.

Currently, some studies in the literature show that using LEV in premature infant seizures is effective and safe for neonates [2,9]. However, studies about the use of LEV in extremely preterm infants with seizures is limited with only a handful studies, the results of which highly vary [4,9,15]. Han et al. [9] conducted a retrospective analysis of 37 preterm infants (mean gestational age 31.5±1.9 weeks (range, 26 to 36+6 weeks)) who were treated with LEV as the first-line anti-seizure medication. That study population included three infants (8%) with extremely low birth weights (less than 1000 g) and 10 (27%) with very low birth weights (less than 1500 g). In their cohort, 57% of all preterm infants were seizure-free while on LEV at the end of the first week, no additional anti-seizure medication was required and they suggested that LEV can be an acceptable and safe choice for treatment of neonatal seizures in preterm infants [9]. Özelkaya et al. [15] retrospectively evaluated 26 preterm infants, including extremely preterm infants (the mean gestational was 26.7±3.3 weeks) treated with LEV. No side effects were observed during LEV treatment. They found that the seizure control rate was 11.5% when LEV was the first-line therapy and overall seizure control rate with LEV was 65%. They reported that seizure control was better achieved when LEV was given as the second antiepileptic medication in premature infants.

A recent study conducted by Kurtom et al. [4], including only extremely preterm infants, evaluated the effectiveness of monotherapy with levetiracetam as a first-line treatment in achieving seizure cessation in extremely preterm infants with seizures. This single-center study retrospectively reviewed 61 extremely preterm infants and showed that 74% of their patients did not respond to LEV monotherapy and required additional medications. Similar with the Kurthom et al. study population, our study included only extremely preterm infants. In contrast to the results of Kurthom et al. [4] and Özelkaya et al. [15] studies, we determined that seizure control was achieved in 60% of all patients, and the rate of seizure control increased to 67% when LEV was first-line treatment. Unfortunately, we could not obtain statistically significant differences between the first-line therapy group and second or third-line therapy groups in terms of the rate of seizures management. It may be related to small sample size of the groups.

The big differences in the rate of seizure control with LEV as first-line therapy between our study and Kurthom's may be related to the most important limitation of our study. They used continuous video electroencephalography to diagnose seizures, but we could not obtain electroencephalography records. Neonatal seizures at the present study were diagnosed based on clinical observation of doctors and nurses. Most likely, in the present study, we may have missed subtle seizures which are known as the most frequently seen seizure type at the neonatal period, due to us using only clinical observation to detect seizures.

Association between SGA and seizures in preterm and term infants has been reported previously [4,8]. Kurthom's study population included an important proportion of SGA patients (21%) and none of them had a favorable response to LEV treatment. We had only two SGA patients and one of them showed a favorable response to LEV treatment, which was used as first line treatment of the seizure. Another factor of differences in the rate of seizure control with LEV as first-line therapy between our study and Kurthom et al.'s study may be related to the low proportion of SGA patients in ours.

No clear recommendations about the dosage of LEV in neonates are available in the literature, where the doses range from 10-80 mg/kg [16-18]. Sharpe et al. [17] showed that LEV was well tolerated in their study of sick neonates and clearance of LEV in neonates was higher than expected on the basis of immature renal function in term infants and increased significantly during the first week of life. At the present study, the seizures were successfully managed by 67% (8/12) when LEV was used as the first-line drug and most of the patients who were given 40 mg /kg loading dosage of LEV as first loading dosage responded well to LEV (10/17 patients, 58%). Some patients needed additional loading dosage to control seizures. The maximal dosage of LEV in our study was 70 mg/ kg/day and no side effects were seen during the loading and maintenance treatment periods. Similar to our results, Han et al. used loading doses of LEV ranging from 40 to 60 mg/kg (mean: 56 mg/kg), the maintenance dosing ranging from 20 to 30 mg/kg (mean: 23 mg/kg) and no adverse effects were observed [9]. Özelkaya et al. [15] used a mean dose of 17±9.23 mg/kg LEV in preterm infants, overall seizure control rate with LEV was 65%, but seizure control rate was 11.5% when LEV was the first-line therapy. Their low efficacy rate of LEV treatment as first-line therapy may be related to lower loading LEV dosage. Although clear recommendations about loading dosage of LEV in premature infants are not available in the literature, according to our results, we think that at least 40 mg/kg loading dosage of LEV may be used to manage seizures successfully at the first loading time.

Limitations

Our study has some important limitations such as small sample size, retrospective design and the diagnosis of seizures being made only clinically, without EEG monitoring. Another important limitation of our study is that patients did not have long-term neurological follow-up. Unfortunately, we could not reach regular follow-up after the discharges of the patients at our neurology department since a significant part of our patients are immigrants or children who are from families with low socio-cultural status. Additional multicentric, larger, prospective randomized control studies are needed to define the efficacy, safety, and tolerability of the use of levetiracetam in extremely premature infants exhibiting seizures during the neonatal period.

Conclusion

Our study indicates that using levetiracetam may be effective in the management of acute neonatal seizures in

extremely preterm infants. Seizure control was better achieved when LEV was given as the first line antiseizure medication for extremely preterm infants. Treatment with intravenous levetiracetam did not result in any important adverse events and was generally well tolerated. We believe that it can be safely used as first or second-line therapy for seizure control in extremely premature infants in the NICU with limited facilities like us, despite all the limitations of our study.

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