JACOBS PUBLISHERS

OPEN ACCESS

Jacobs Journal of Pediatrics

Research Article

I.V. Levetiracetam versus Phenobarbitone in Neonatal Seizures A Randomized, Single Blind Prospective Clinical Trial

Adel A. H. Mahmoud[1] FRCP, MRCPCH, Ayman Tagelsir Abdalla[2] SSC Ped, SF Neo, Ahmed M. A. Elajab[3] MD, MRCPCH, Ahmed A. Mansy[4] MSc, M.D

[1] *Consultant Pediatric Neurologist, Pediatric Neurology Department, National Neuroscience Institute King Fahad Medical City, Riyadh Saudi Arabia*

[2]*Consultant Neonatology, Pediatric Hospital-NICU, King Saud Medical City, Riyadh Saudi Arabia*

[3]*Pediatrics and Neonatology, SSR-Neonatology Department, UAE-Dubai-AlJalila Specialized Children Hospital, United Arab Emirates*

[4]*Pediatric Department, Consultant Pediatric Neuroogist, Pediatric Department Royal Commission Hospital, Jubail Saudi Arabia*

**Corresponding author: Adel A. H. Mahmoud FRCP, MRCPCH , Consultant Pediatric Neurologist, Pediatric Neurology Department, National Neuroscience Institute King Fahad Medical City, Riyadh Saudi Arabia, Post Code 11393, POB 365814, Tel: 00966543376723; Email: amahmoud2000@hotmail.com*

Received: 12-01-2015

Accepted: 01-28-2016

Published: 02-18-2016

Abstract

Objective: Seizures in neonates are relatively common. Only few studies are available about the safety and efficacy of antiepileptic drugs used for treatment of neonatal seizures. The standard treatment has been Phenobarbitone (PB). Usually it is given as intravenous (I.V.) and followed when it is successful, by the oral form. Recently Levetiracetam (LEV) was studied with promising results. Here we compare the safety and efficacy of LEV with PB in the treatment of neonatal seizures.

Methods: This is a randomized single blind study conducted at King Fahd medical city: a tertiary care hospital in Saudi Arabia between 2008 and 2015. The Institution Review Board approved the study. Parental agreement was obtained by signing informed consent prior to participation in the study.

It is monophasic 22 neonates (birth to 28 days of age) with clinical seizures were recruited from the Neonatal Intensive Unit. They were randomized into 2 groups, group1 or 2, utilizing one of the readily available programs of randomization on the Internet.

Group 1: treated with I.V. PB with possible switch to I.V. LEV if the former fails, while group 2 treated with I.V. LEV with possible switch to PB if the former fails.

Treatment was randomly chosen and given by the Neonatal Intensive Care nurse as prescribed by physician on duty (patients do not know which drug is used). Seizure classification was adopted from Volpe.. Clinical detection was the essence of diagnosing seizures. This reflected practical choice due to the non-availability of handy electroencephalograms (EEGs).

Results: The efficacy of both drugs in treating seizure showed that 3 of 10 (30%) neonates from those who received LEV as first line therapy needed to receive other antiepileptic drugs to control the seizures. Meanwhile, 2 neonates out of 12 who

received PB as first line therapy needed to get either LEV alone or with addition to phenytoin after one day.

Several side effects were observed among the PB group as hypoglycemia, high renal profile associated with high Creatinine level and hyponatremia as Na 121. But only CBC abnormality as neutropenia was noticed in the LEV group and no other reason was suggested.

Significance: Both drugs PB and LEV were found to be effective in abolishing neonatal seizures.

In our small sample the efficacy of LEV was 70% as it was effective in controlling all seizures in 7, while it needed the addition of PB with and without PHT in 3 (30%).

Efficacy was 83% with 10 patients not needing another drug, while 2 neonates needed one drug in one patient and two drugs in the other to control their seizures.

The side effects were more on the side of PB. So in this small sample study we conclude that both LEV and PB were effective with relative superiority of PB regarding efficacy and relative superiority of LEV regarding safety

Introduction

Seizures in neonates are relatively common, with variable clinical manifestations. Most of the time they are of earliest signs of neurological dysfunction, and they may predict long-term cognitive and developmental sequalae [1].

The effects of neonatal seizures on the immature brain are difficult to distinguish from those of the brain lesions causing them, however the presence of prolonged seizures in the neonatal period represents an important risk factor for poor prognosis or developing neurological sequelae. The mortality risk is still high (22-58%) in preterm births despite its reduction in term babies (7 to 16%) and the overall risk of impairment following neonatal seizures is still as high as 30% [2].

Early neonatal seizures are more common than those occurring later in infancy.

Aim of treatment of neonatal seizures may be variable; but usually it is aimed at ruling out immediately treatable causes, decreasing risk of seizure induced central nervous system injury as well as decreasing detrimental effects of seizures on other systems.

The standard treatment for neonatal seizures has been and still is phenobarbitone. Usually it is given as I.V. and followed when it is successful, by the oral form [3].

Unfortunately there are only few studies about the safety and efficacy of the commonly used antiepileptic drugs.

Comparison between PB and Phenytoin (PHT) revealed that both drugs were comparable regarding efficacy reaching about 43% for either drug alone and up to 59% seizure control if both drugs are combined [4].

In addition to limited efficacy data for PB, there is concern for both its short-term and long-term adverse effects on development [5].

A recent study discussed the efficacy of LEV in neonatal seizures. 12 patients received a load of 25 to 50 mg/kg. 9 of 11 the neonates (82%) reached seizure cessation within 24 hours of receiving LEV. No serious side effects were evident. 7 patients (59%) were discharged on oral LEV alone, 4 (33%) were discharged on no oral antiepileptic drugs, and 1 (8%) was discharged on LEV and PB [6].

A report summarized data from 19 neonates with clinical seizures treated with LEV.

15 were previously treated with PB, and 4 had LEV as first line therapy. After initial doses of 4 to 42 mg/kg in the first 24 hours, maintenance doses of 25 to 90 mg/kg/day were achieved. Transient sedation occurred in 3 and 2 discontinued due to sedation and irritability, respectively. 3 infants who had failed numerous other medications had no response to LEV. 11 (58%) became seizure free. Of 8 patients who discontinued anti-epileptic drugs, 7 remained seizure free with a follow-up of 34 to 57 months. 6 patients who continued on LEV were reported to have “excellent” seizure control for a follow-up of 9 to 45 months [7].

These promising results support the importance of doing prospective controlled trials of LEV in neonates.

Another study showed the freedom of seizures in 30 infants under LEV at the end of the first week with 27 remaining seizure free at four weeks while EEGs markedly improved in 24 patients at 4 weeks. In 19 cases, LEV was discontinued after 2-4 weeks, while 7 infants received LEV up to 3 months. No severe adverse effects were observed [8].

2 case reports of LEV use in neonates described a neonatal case of “malignant migrating partial seizures in infancy” in a patient who was unresponsive to Clonazepam, PB, and Lamotrigine. Subsequently, he had a positive response to LEV, which was not started, however, until 5 months of age. An initial dose of 10 mg/kg/day was increased to 30 mg/kg/day and continued for 14 months [9].

Another report described the use of LEV in 3 infants, aged 2 days to 3 months, for refractory seizures or intolerance to other anticonvulsants. One patient was started on LEV at a 60

mg/kg orogastric bolus, followed by a maintenance dose of 30 mg/kg/day. LEV was initiated at 30 mg/kg/d in the other 2. The infants were seizure-free on LEV mono-therapy during follow-up intervals ranging from 2 to 18 months. No adverse events were reported [10].

Other report analyzed 22 neonates; 12 females and 10 males with partial epilepsy who received I.V. LEV.

19 patients (86%) experienced immediate seizure control within one hour of the loading dose. These patients responded to I.V. LEV both electrographically and clinically with improvement seen one hour after commencing the loading dose. No further seizures were recorded while on I.V. LEV in 7 (32%) of neonates after loading. 14 patients (64%) achieved seizure freedom on I.V. LEV within 24 hours of the loading dose, 19 (86%) within 48 hours, and 22 (100%) within 72 hours [11]. Levetiracetam's efficacy and safety has been confirmed in different age groups.

110 children with refractory epilepsy were evaluated. The children included 21 aged <4 years. LEV was effective (>50% decrease in seizure frequency) in 39% of children, of whom 10 (9%) became seizure-free. The median follow-up period was7 months. LEV was well tolerated. The main side effects of somnolence and irritability occurred in 14% of patients. In one patient, acute choreoathetosis occurred after few doses of LEV. The adverse effects were generally tolerated. Children younger than 4 years were particularly tolerant. The authors concluded that LEV might be a valid therapeutic option for epilepsy in infants and young children [12].

26 children age 10 years and under with refractory epilepsy were retrospectively studied to evaluate the efficacy and safety of LEV.

61% of patients showed a good response to LEV (≤50% reduction in seizure frequency), of whom 2 (8%) with previously refractory epilepsy became seizure-free. LEV was well tolerated with very few reported side effects [13].

In 81 children younger than 4 years of age with refractory epilepsy studied in multi center retrospective study with follow up period of 9 months, LEV was found to be effective in 30% of patients (response >50% of seizure reduction, 12% of those became seizure free).

34% of patients showed adverse effects mainly drowsiness and nervousness.

Adverse events were either tolerable or resolved with time with dosage reduction or discontinuation of the drug [14].

Regarding tolerability and dosing experience of IV LEV in children and infants, our institute experience revealed that high doses LEV (whether as loading or maintenance) were safe and tolerable (unpublished data).

15 children <14 years of age were studied using I.V. LEV.

Among those, 6 patients were < 4 years of age (they received 82/118 infusions) with initial dosing average 13.8 mg (12-15.6) and maintenance dose average 26.5 mg with (5-43) mg/kg/day.

No side effects were noticed during the 15 minutes infusion; but while on the maintenance dose, one patient among the group <4 years reported agitation and modest decrease in white blood cell count [15].

Methods

This is a randomized single blind study conducted at the Pediatric Neurology Department, National Neuroscience Institute King Fahad Medical City, a tertiary care hospital in Riyadh, Saudi Arabia between first of January 2008 and 30th of June 2015. The Institution Review Board approved this study. Parental agreement was obtained by signing informed consent prior to participation in the study.

It is monophasic 22 neonates (birth to 28 days of age) with clinical seizures were recruited from the Neonatal Intensive Unit. They were randomized into 2 groups, group1 or 2, utilizing one of the readily available programs of randomization on the Internet.

Group 1: treated with I.V. PB with possible switch to I.V. LEV if the former fails, while group 2 treated with I.V. LEV with possible switch to PB if the former fails.

The diagnosis of the 2 groups were clinically based adopting Volpe classification [16].

Because EEG is a facility not always available, and as lack of consistent electrographical correlates from surface recorded EEG findings does not rule out an epileptic process[16], we elected to choose clinically based seizures for the trials of treatment.

As electroclinical dissociation is well known in newborns[17] we considered recruiting those babies with clinically confirmed seizures. The rare type of generalized tonic clonic seizures was the one affecting all our babies. This was a kind of unexpected finding; but it reflected how undoubtedly the conditions were true seizures and not any of the mimickers. This might be thought to be a limitation; but the aim of the study was to compare efficacy of 2 drugs in treating detected seizures and not to detect or estimate the occurrence of seizures

in this age group.

Treatment was randomly chosen and given by the Neonatal Intensive Care nurse as prescribed by physician on duty (patients do not know which drug is used).

The intravenous form of either drug was continued until it is possible for the baby to take orally.

No exclusion criteria were applied. Instead, if failure of a drug or adverse events occurred, the baby was switched to the other drug and this would be analyzed at the end of the study.

The drug was considered failure if it could not stop at least 50% of the neonate seizures in 24 hours (50% of duration of all the seizures per 24 hours).

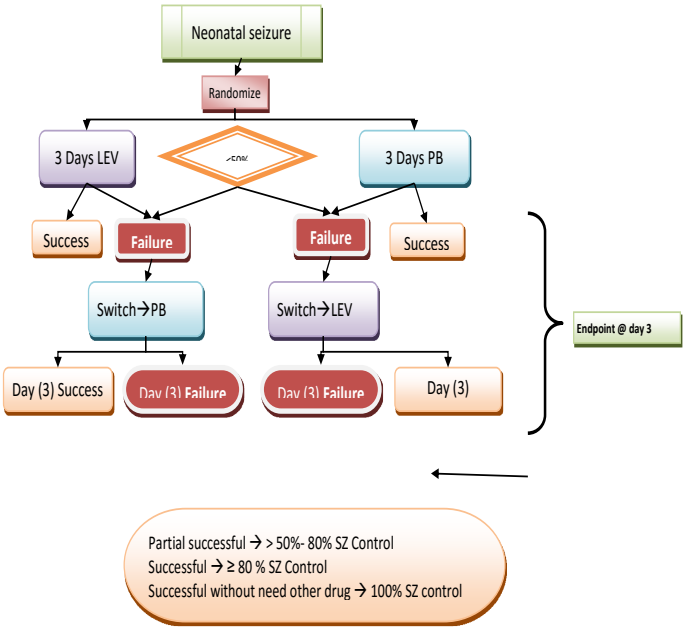
It was considered partially successful if it controlled 50-80% of the seizures, and successful if it controlled ≥ 80% but less than 100% of the seizures, or successful without need to other drugs if it controlled 100% of the seizures.

The dose of PB was started as I.V. loading 10-20 mg /kg over 10-20 minutes. The dose could be repeated up to 40-60 mg/ kg loading (as recommended by previous studies [18,19].

On the other hand, the dose of LEV was started at I.V. 10 mg/kg and could be increased up to 50 mg/kg [20].

Each drug was evaluated based on the endpoint; which was the rate of seizure cessation after 3 days on treatment (Figure 1).

Figure 1. The study protocol of the use of IV PB or IV LEV for neonatal seizures.



Safety and tolerability endpoints:

Tolerability measures included adverse events (AEs), defined as any untoward medical occurrences reported by investigators at any time during the study.

Adverse events would be reported regardless of their cause.

Safety was assessed on the basis of AEs, physical and neurologic examinations, vital signs, and clinical laboratory tests.

Adverse events were rated as mild, moderate, or severe, and serious AEs according to International Co-operation on Harmonisation (ICH) standards.

Adverse events categories were based on the International Medical Nomenclature/International Therapy Dictionary.

Pretreatment assessments and procedures:

1. Medical history included pregnancy, perinatal, and family history information.

2. Comprehensive general, systemic, and neurologic examination was done.

3. Blood work included:
   a. Blood glucose.
   b. Urea and electrolytes.
   c. Liver and thyroid function tests.
   d. Blood gases
   e. Metabolic screening.
   f. Electroencephalography.
   g. Cranial ultrasound
   h. Neuroimaging (CT/MRI brain)

4. Daily:
   A) Seizure chart.
   B) Adverse events
   C) As indicated:

Blood ammonia, acylcarnitine, and lactate

Results: Data were represented as number either percentage or mean+- SD.

The Demographic characteristics of the neonates where comparable in the two groups in regards to the gestational age.

However, the birth weight was relatively higher in the PB group (3097.4+1040.5) versus (2087+1173.7) and the head circumference was lower in the LEV group (30.8 ±5.12) versus (35.83±6.79) (Table1).

Table 1. Demographic characteristics in LEV and PB

Characteristics	LEV Group (n = 10)	PB Group (n = 12)	P – value
Gestational age (week)	38.7 ± 16.46	37 ± 4.30	0.733
Birth weight (kg)	2087 ± 1173.7	3097.4 ± 1040	0.044
Head circumference (cm)	30.8 ± 5.12	35.83 ± 6.79	0.068
Mode of delivery Vaginal c/s	 2 (20%) 8 (80%)	 7 (58.33%) 5(41.6%)	0.068

The maternal medical history of the included neonates in LEV group included hypertension, gestational Diabetes, and Urinary tract infection (40%) compared to 25% in PB arm that were represented by Hepatitis B+ve, Hypertension, Gestational Diabetes Mellitus, and Systemic Lupus Erythematosus/ Group B Streptococci .

Unlike LEV group, where the fetal movement during pregnancy was normal in 100%, the PB group, fetal distress was recorded in 4 (33.3%) (Table 2)

50% and 58.33% in the LEV and PB respectively showed neurological abnormalities.

The LEV group involved more patients with hydrocephalus and hypotonia (Table 3).

The seizure attack was categorized based on age onset, type, frequency and duration.

Tonic-clonic was the main type that both groups experienced.

Table 2. Maternal data in LEV and PB (n=22)

Characteristics	LEV Group N=10(%)	PB Group N=12 (%)	P – value
Age (year)	30 ± 6.3944	31 ± 4.541	0.669
Amniotic fluid	Normal 10(100%)	Normal 11 (91.6%) Meconium 1(8.4%)	0.350
Illness Yes N0	4 (40%) (HTN, Gestational DM,UTI) 6(60%)	3(25%) (Hep. B+ve, HTN ,Gest DM,SLE/GBS) 9(75%)	0.452
Medication Yes	2 (20%) antihypertension antibiotics	2 (16.66%) antihypertension antibiotics	0.840
APH Fetal movement Normal Fetal distress	 10 (100%) 0.0	 8(66.66%) 4(33.33%)	0.0435

Prematurity was the main cause of admission in LEV group (40%), while it was the congenital anomaly in PB group (41.66%), although no significant difference in number of cases of prematurity and babies with congenital anomalies in both groups. (Table 3)

The neonates in LEV group experienced seizure as early as one day old or as late as 67 days. While in PB arm, most of the neonates suffered from seizures within hours of delivery: 41.66% between 2-5 days and in 33% onset reached 38 days. There were more neuroimaging abnormalities in the PB group 10 (83.3) compared to 6(60) in LEV arm (Table 4).

Table 3. Clinical data on LEV and PB

	LEV Group (n = 10)	PB Group (n = 12)	P – value
Cause of admission	Prematurity 4 (40%) Congenital anomalies 3(30%) Respiratory distress 2(20%) Sepsis 1(10%)	Prematurity 3 (25%) Congenital anomalies 5 (41.66%) Seizure 3 (25%) Sepsis 1 (8.33%)	0.881
Dysmorphism and Structural Abnormalities Yes No	4 (40) 6 (60)	4 (33.3) 8 (66.66)	0.746
Neurological abnormalities None Present as	5 (50%) Hydrocephalus 3 (30%) Hypotonia 1(10%) Spina bifida 1(10%)	7 (58.33%) Hydrocephalus 2(16.6%) Dilated bilat ventricles 1(8.33%) Ventriculomegaly 1(8.33%) Wide anterior fontanel spina bifida 1(8.33%)	0.785

Table 4. Seizure, neuron imaging and EEG of patients in LEV arm

	LEV Group (n = 10)	PB Group (n = 12)	P – value
Onset age 1 day or less 2 -5 days >10 days	6 (60%) 1 (10%) 3(30%)	5 (41.66%) 4 (33.33%) 3 (25%)	0.425
Type Tonic-clonic	10 (100%)	12(100%)	1.000
Frequency 1time 2times 3 times 4 times	7 (70%) 2(20%) 0.0 1 (10%)	7 (58.33%) 2 (16.66%) 1 (8.33%) 2 (16.66%)	0.762
Duration	Less than 30 seconds: 3(30) 30 seconds: 4(40) 60 seconds: 3 (30)	Less than 60 second: 8(66,6) 60 seconds: 1(8.3) More than 60 seconds: 3(25)	0.146
Neuro imaging abnormalities None Present	4(40%) 6 (60%)	2(16.6%) 10(83.3%)	0.221
EEG	None 4 (40%) Done 6 (60%)	None 5 (41.6%) Done 7 (58.33%)	0.936

The efficacy of both drugs in treating seizure showed that 3 of 10 (30%) neonates from those who received LEV as first line therapy needed to receive other antiepileptic drugs to control the seizures. Meanwhile, 2 neonates out of 12 who received PB as first line therapy needed to get either LEV alone or with addition to phenytoin after one day (table 5).

Table 5. Switch to another medication.

	LEV Group	PB Group	P – VALUE
Need for other medication	7(70%): no need for other drug 3(30%): needed PB	10 (83.33%): no need for other drug 1 (8.33) needed: LEV+PB +Phenytoin 1 (8.33) needed PB+LEV	0.306
LFT abnormalities Present	0.0	4 (33.3%)	0.195
CBC abnormalities Abnormal	5(50)	2 (16.66)	0.226

Several side effects were observed among the PB group as hypoglycemia, high renal profile associated with high Creatinine level and hyponatremia as Na 121. But only CBC abnormality as neutropenia was noticed in the LEV group and no other reason was suggested.

Discussion

Neonatal seizures are serious health conditions. They might lead to a delay in the neurological development in brain. Proper management of those cases leads to significant outcome change [21].

Despite the fact that antiepileptic medications are not well investigated in terms of safety especially in neonates, PB has been used for long time [22]. Its safety profile is low compared to some other antiepileptic medications [22].

As supported by other studies, LEV has more favorable safe profile in terms of side effects compared to PB [23].

The purpose of this pilot study is to gather information about the efficacy and safety of PB and LEV in neonates. The small sample size of the study was accepted based on the purpose to assess the feasibility of larger experiment.

The rarity of generalized tonic clonic seizures due to cerebral immaturity [16] reflects the accuracy of having real seizures and not conditions mimicking seizures. This is important as the aim of the study is not how best to diagnose or capture all seizures; but to compare between 2 drugs regarding their efficacy of treating confirmed seizures.

Of importance is to mention that the response to either drug was clinically based; but babies' clinical manifestations that reversed completely and general condition that had improved with cessation of seizure and autonomic manifestations left no doubt that those seizures were truly responding. In reality we followed those babies with EEGs to determine when to stop the treatment; but that was not a part of the study.

Further studies on large scales are needed to support our findings and to confirm our results.

The demographic, maternal data, clinical, neuroimaging information, response and side effects of the medication were collected. There was no significant difference in demographic and maternal features in both groups. The clinical diagnosis, time of the first seizure, neuroimaging findings and underlying congenital malformation were more or less comparable.

Conclusion

Both drugs PB and LEV were found to be effective in abolishing neonatal seizures.

In our small sample the efficacy of LEV was 70% as it was ef-

fective in controlling all seizures in 7, while it needed the addition of PB with and without PHT in 3 (30%).

Efficacy of PB was 83% with 10 patients not needing another drug, while 2 neonates needed one drug in one patient and two drugs in the other to control their seizures.

The side effects were more on the side of PB. So in this small sample study we conclude that both LEV and PB were effective with relative superiority of PB regarding efficacy and relative superiority of LEV regarding safety.

Acknowledgement

We acknowledge the contribution of Dr. Aqeela Al Hashim, Pediatric Neurologist, Dr. Fahad Al Aql, Neonatologist, Ms. Maryam Al Khalaf, Research Coordinator, Mr. Muhammad Salman Bashir, Biostatistician, Dr. Mohammad Al Tannir, Head of Research & Scientific Publication Center, King Fahad Medical City, Riyadh, Saudi Arabia for their input and also Ms. Samar A Mahmoud for her effort in organizing the article for appropriate submission and our secretary Levina Tiongco whose effort was undoubtedly invaluable.

Disclosure: The authors have not disclosed any affiliation or financial involvement with organizations or entities with a direct financial interest in the subject matter or materials discussed in the manuscript. No funding was received for this work from any organization).s

References

1. Nunes ML1, Martins MP, Barea BM, Wainberg RC, Costa JC. Neurological outcome of newborns with neonatal seizures: a cohort study in a tertiary university hospital. 2008, 66(2A): 168-174.

2. Spagnoli C, Pavlidis E, Pisani F. Neonatal seizures therapy: we are still looking for the efficacious drug. Italian Journal of Pediatrics. 2013, 39: 37.

3. Bartha AI, Shen J, Katz KH, Mischel RE, Yap KR et al. Neonatal seizures: multicenter variability in current treatment practices. Pediatr Neurol. 2000, 37: 85-90.

4. Painter MJ, Scher MS, Stein AD, Armatti S, Wang Z et al. Phenobarbital compared with phenytoin for the treatment of neonatal seizures. N Engl J Med. 1999, 341: 485-489.

5. Hahn CD, Riviello JJ. Neonatal Seizures and EEG: Electroclinical Dissociation and Uncoupling. Neo Reviews. 2004, 5(8): e350-355.

6. Khan O, Cipriani C, Wright C, Crisp E, Kirmani B. Role of Intravenous Levetiracetam for Acute Seizure Management in Preterm Neonates. Pediatric neurology. 2013, 49(5): 340-343.

7. Wical BS, Ritter FJ, Norberg SK. Levetiracetam use in neonates: safety, tolerability, and long-term outcome. Epilepsia. 2005, 47(S4): 186-187.

8. Ramantani G, Ikonomidou C, Walter B, Rating D, Dinger J. Levetiracetam: Safety and efficacy in neonatal seizures. European Journal of Paediatric Neurology. 2011, 15(1): 1-7.

9. Hmaimess G, Kadhim H, Nassogne MC, Bonnier C, van Rijckevorsel K. Levetiracetam in a neonate with malignant migrating partial seizures. Pediatr Neurol. 2006, 34(1): 55-59.

10. Shoemaker TM, Rotenberg JS. Levetiracetam for the treatment of neonatal seizures. Journal of Child Neurology.2007, 22(1): 95-98.

11. Khan O, Chang E, Cipriani C, Wright C, Crisp E et al. Use of intravenous levetiracetam for management of acute seizures in neonates. Pediatr Neurol. 2011, 44(4): 265-269.

12. Grosso S, Cordelli DM, Franzoni E, Coppola G, Capovilla G et al. Efficacy and safety of levetiracetam: An add-on trial in children with refractory epilepsy. Seizure. 2005, 14(4): 248-253.

13. Tan MJ, Appleton RE. Efficacy and tolerability of levetiracetam in children aged 10 years and younger: a clinical experience. Seizure. 2004, 13(3): 142-145.

14. Grosso S, Cordelli DM, Franzoni E, Coppola G, Capovilla G et al. Efficacy and safety of levetiracetam in infants and young children with refractory epilepsy. Seizure. 2007, 16(4): 345-350.

15. Michaelides C, Thibert RL, Shapiro MJ, Kinirons P, John T et al. Tolerability and dosing experience of intravenous Levetiracetam in children and infants. Epilepsy Res. 2008, 81(2-3): 143-147.

16. Volpe JJ. Neurology of the newborn. 5th ed, Philadelphia, WB Sanders, 2008.

17. Clancy RR, Legido A, Lewis D. Occult neonatal sezires. Epilpesia. 1988, 29: 256-261.

18. Rennie JM1, Boylan GB. Neonatal seizures and their treatment. Curr Opin Neurol. 2003, 16(2): 177-181.

19. Boylan GB, Rennie JM, Pressler RM, Wilson G, Morton M et al. Phenobarbitone, neonatal seizures, and video-EEG. Arch Dis Child Fetal Neonatal Ed. 2002, 86: F165-F170.

20. Aceves J, Khan O, Mungall D, Fonkem E, Wright C et al. Effi-

cacy and Tolerability of Intravenous Levetiracetam in Children. Front Neurol. 2013, 4: 120.

21. Frances E. Jensen, MD. Neonatal Seizures: An Update on Mechanisms and Management. Clin Perinatol. 2009, 36(4): 881.

22. Nathalie L Maitre, Ciaran Smolinsky, James C. Slaughter, and Ann R Stark . Adverse neurodevelopmental outcomes after exposure to phenobarbital and levetiracetam for the treatment of neonatal seizures. J Perinatol. 2013, 33(11): 841-846.

23. Abend NS, Gutierrez-Colina AM, Monk HM, Dlugos DJ, Clancy RR. Levetiracetam for Treatment of Neonatal Seizures. Journal of Child Neurology. 2011, 26(4): 465-470.