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Effect of Levetiracetam in the Treatment of Refractory Seizure in Infants through EEG: The Case of the Neonatal Intensive Care Unit of Tehran's Children's Medical Center

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Authors' contributions

This work was carried out in collaboration between all authors. Authors MK, MM and Reza Shervinbadv designed the study, performed the statistical analysis, wrote the protocol and wrote the first draft of the manuscript. Authors ZM, Raziee Sangsari and BY managed the analyses of the study. All authors read and approved the final manuscript.

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ABSTRACT

Objective: Phenobarbital, phenytoin and Benzodiazepins are the most common treatments for resistant neonatal seizure [1]. Drug of choice in the treatment of neonatal seizure should be more effective and have fewer side effects. This study examines the effect of Levetriacetam (LEV) in the treatment of resistant neonatal seizure, using EEG (electroencephalogram).

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Methods: This is a clinical trial study that lasted 1 year, from March 2016 to March 2017.
20 neonates with early detection of seizure were hospitalized at the NICU of Children's Medical Center in Tehran. These neonates included both term and preterm neonates over 30 weeks and more than 2000 gr, who did not respond to a single dose of Phenobarbital and Phenytoin. The results of statistical tests were analyzed and significant level was considered ($p<0.05$).
Results: 85% of the patients were male with average age of 13 days. The most common cause of seizure in 45% cases was Hypoxic-Ischemic Encephalopathy (HIE). 65% of the newborns were seizure free after 24 hours of taking LEV whereas 80% of them after 72 hours. The 3 neonates who did not respond to LEV were endotracheal intubation. The average loading dose of LEV was 32±10.5, and the average maintenance dose was 18±8.3. No side effects were observed in using LEV.
Conclusion: The findings of this study suggest that LEV is effective in unresponsive seizure to Phenobarbital and Phenytoin. It can, equally, reduce seizure frequency in newborns. Due to very low side effects and transient, it can also be used as a second-line therapy in the treatment of resistant neonatal seizure. However, multi-centered studies with a higher sample volume in the form of clinical trial are needed for further investigations on this topic.

Keywords: Seizure; neonate; EEG; levetriacetam.

1. INTRODUCTION

Seizures in infancy are more common than any other times in life [2,3]. The prevalence of neonatal seizure is 1.48.6 of every 1000 live births [4,5]. It is difficult to estimate the incidence of neonatal seizures since it depends on the studies of population status and characters in seizure diagnosis and various statistical samples. At this time, seizure has associated with epilepsy risks and neurodevelopmental delays [6]. The most common causes of seizure in infants are Hypoxic-Ischemic Encephalopathy, central nervous system infection, cerebral hemorrhage and genetic and metabolic disorders [7].

In spite of a lack of guidelines for the treatment of neonatal seizures, Phenobarbital is commonly used as the first-line treatment for neonatal seizures [8]. However, old anticonvulsants such as Phenobarbital, Benzodiazepines and Phenytoin have drug interactions and side effects [9]. Resistance to them has caused the use of second- and third-line drugs [8]. In spite of limited drug information and FDA'S disapproval, LEV is used as the second-line anticonvulsant [10-12]. LEV is a newer anticonvulsant drug with a novel mechanism of action [13]. It binds to the Synaptic Vesicle Protein (SV2A) within the brain, and this binding impedes neurotransmitter release [14]. Since 2006, LEV has been approved for the seizure treatment for patients below the age of 16. [15]. It is a safe and effective drug in treating neonatal seizures. However, it may not work well in the most sever hypoxic ischemic encephalopathy [16]. LEV is quickly absorbed from digestive system and to limited extent adjoins to plasma proteins and its half-life is about 8 hours [14]. It has renal excretion and no significant drug interactions [17,18]. No severe or life threatening side effects of this drug has been reported [15,19,20]. In infants, only case studies, pharmacokinetics studies and some controlled trials (RCTs) are available, which suggest relatively good efficacy. Many of the above-mentioned studies do not include EEG monitoring [8].

Due to the importance of choosing the right seizure drug in a way to have the highest effect and the least side effects, we have set out to investigate the efficacy of levetriacetam in refractory status epilepticus in infants through EEG in the neonatal intensive care unit.

2. METHODS

This research is a clinical trial study on 20 hospitalized neonates in an intensive care unit at Tehran's Medical Center Subspecialist Hospital. This study lasted 1 year, from March 2016 to March 2017 and was approved by the medical sciences ethics committee at the University of Tehran. The admission rate was nearly four hundred people per year in the neonatal intensive care unit, accounting for about 20% of seizures.

Convenient sampling was used in this study. Sampling involved observations, interventions, evaluations and questionnaires. Data was collected by clinical examinations and observations. Detection of seizures was based

on direct observation of the relevant doctor in charge or the pediatrician fellowship using video EEG, whose results were interpreted by a pediatric neurologist. Information of infants was extracted by filling a questionnaire and using and records of parents. All information was confidential and encoded.

After the adaption to research and necessary coordination with explanation, informed and written consent forms were obtained from parents. Preterm and term infants with a gestational age of 30 weeks with a weight of more than 2000 g, who did not respond to anticonvulsant—such as Phenobarbital with single loading dose (20 mg/kg) and Phenytoin (20 mg/kg)—were chosen. If the seizure did not respond to these two drugs, LEV with loading dose of 10 mg/kg was used at the start, and if there was no response to seizure, this amount was repeated after every 10 to 15 minutes with a higher dose, up to 50 mg/kg. If no response was shown after the maximum permissible dose, then, Midozolam was used. In case of seizure response to Levetiracetam, the treatment (20 mg/kg phenobarbital and 20 mg/kg phenytoin and Levetiracetam based on the dose by which seizure was controlled) continued as a maintenance dose up to 30 mg/kg.

End seizure means complete cessation of seizure 10 minutes after acute infusion completion, which does not reoccur within 12 hours. The information obtained from patients were as follows: age, sex, birth weight, gestational age (G.A), etiology, family history of epilepsy, attributed to parents, apgar score at 1 and 5 minutes of birth, frequency of seizure before hospitalization, anti-epileptic drugs prescribed during seizure with their doses, controlling seizure 24 and 72 hours after starting treatment with LEV, drugs side effects, EEG findings and neuroimaging. The excluding criteria of the research participants of the present study were these: infants whose seizure responded to Phenobarbital and Phenytoin, infants whose seizure was caused by hypoglycemia, hypocalcemia, hypomagnesemia and responded to generic treatments by sugar, calcium and magnesium correction, infants who had received other anti-epileptic drugs except Phenobarbital and Phenytoin prior to starting LEV, infants who had received more than a single dose of Phenobarbital, and lastly, infants whose parents did not agree their children to take part in this study.

Cardiorespiratory monitoring and vital signs study— such as heart rate, respiratory rate, temperature and blood pressure—were performed for all neonates and side effects were recorded after starting LEV. Neonatal seizure diagnosis was through clinical observation and video EEG, which was interpreted by a pediatric neurologist. The aim was to control clinical seizure after treatment with LEV and EEG were taken at the time of starting the LEV or later, for there was only one EEG monitoring device for all infants in our NICU; therefore, it was impossible to use the device for several infants at the same time. The improvement of electrographical seizure has been with disappearance ictal pattern but interictal pattern could still be seen. Laboratory tests used in this study included: complete blood count, liver and kidney function, electrolytes and arterial blood gas. Depending on the conditions of the infants, some of them were taken metabolic tests. Neuroimaging was done also based on the clinical situation.

Sample size was calculated using 0.05 alpha value and 80% power and considering the ratios of 0.0001 and 0.5; the sample size was initially set at 15, which was later increased to 20 due to availability of patients. Data was analyzed by using frequency and percentages. Data analysis was performed using SPSS software version 20 that significant level was considered $\alpha=0.05$ and also T-test and Chi-squre were statistical tests.

3. RESULTS

20 infants were included in this study, of whom 17 (85%) responded to LEV. The 3 others who did not respond to LEV were treated with Midozolam afterward. Of the 17 infants, 14 (85%) were boys and 3 (15%) were girls. Average hospitalization time was 13 days (standard deviation of 10.5 days and domain of 1-29 days). Delivery method of 75% was by Cesarean section and others 25% by natural birth.10% of the infants had family history of seizure in first degree relative. 35% of the infants had no seizure prior to hospitalization, 45% had less than 5 times and 25% had more than 5 times seizure prior to hospitalization. 12 infants (60%) had attributed parents. The most common reason for seizure was hypoxic ischemic encephalopathy (45%). The vascular brain lesions and brain hemorrhage (20% of infants) were the second common cause as summarized in Table 1. The results of HIE groups are summarized in Table 2.

Table 1. Etiologic distribution of neonatal seizure

Diagnosis	Number	percent
Hypoxic ischemic encephalopathy	9	45
Brain vascular lesion(ICH and Infarct)	4	20
Sepsis and Meningitis	2	10
Resistant electrolye imbalance	1	5
Inborn Errors of Metabolic	2	10
Aquired metabolic encephalopathy	1	5
Idiopathic	1	5

ICH: Intracranial Hemorrhage

Gestational age in 65% of infants was over 37 weeks and the means of gestational age was 37 weeks and 3 days. Birth weight in 70% was above 2500 g. 90% of neuroimaging finding were abnormal that the most abnormal findings 40% is related to Hypoxic changes and periventricular leukomalacia. Brain Hemorrhage and infract 25%, brain edema 15%, brain abscess and Hydrocephalus were 5%. EEG findings in 15 cases (75%) were abnormal. Two samples of infant's neuroimaging are presented in Figs. 1-3. Of all 17 infants which seizure control with LEV, in 12 infants background activity of EEG were being normal and in 5 of them ictal pattern disappeared but there have been interictal pattern including sharp focal and focal spikes and genrelized epileptiform discharge. EEG diagrams of two infants are shown in Figs. 4, 5. Moratality in two infants (10%) were due to Hypoxic-Ischemic encephalopathy and metabolic diseases. The average loading dose of intravenous levetriacetam was 32.5±10.5 mg/kg and the average maintenance dose was 13±8.3 mg/kg/day.

3.1 Comparison of Variables between Responder and Nonresoponder Groups

During hospitalization, 7 infants (35%) had tracheal intubation from which all 3 infants who did not respond to LEV were intubated, but in 13 cases (65%) who did not have intubation, all were infants who had responded to LEV. Tracheal intubation in infants who did not respond to LEV was more than infants who did respond to the treatment, and there was a meaningful connection (p=0/03,<0.05). 13 infants (65%) had no seizures after 24 hours from which all 13 cases (76.5%) where those who responded to LEV, and in the non-responding group all 3 infants (100%) had continious seziure. Repetition of seizure after 24 h in infants who did not respond to LEV was higher than those who did, and there was a meaningful connection (P=0.03 & <0.05). 80% of infants had no seizure after 72 hours, where 82.4% were in the responder group and 66.7% were in the non-responder group, and had no meaningful connection. No other meaningful connection was present in terms of other variables (Table 3).

Table 2. Results in HIE groups (n=9)

Variables	Numbers
Response to LEV (n)	
Yes	8
No	1
Sex(n)	
Boy	7
Girl	2
GA(n)	
<37w	2
>37w	7
Nouroimaging (n)	
NL	1
Hypoxic changes and periventricular leukomalacia	8
Mortality (n)	1
Number of seizure	
Before LEV(n)	
NL	3
<5	4
>5	2
EEG	
Before treatment(n)	
NL	1
Abnormal	8
EEG	
After treatment(n)	
NL	4
Abnormal	5

EEG: Electroencephalogram

4. DISCUSSION

LEV is a newer anticonvulsant drug. Because of a lack of neurotoxic side effects in LEV and the reduction of apoptotic cells in the brain hippocampus in animal models, LEV has commonly been used for the treatment of neonatal seizure [21,22].

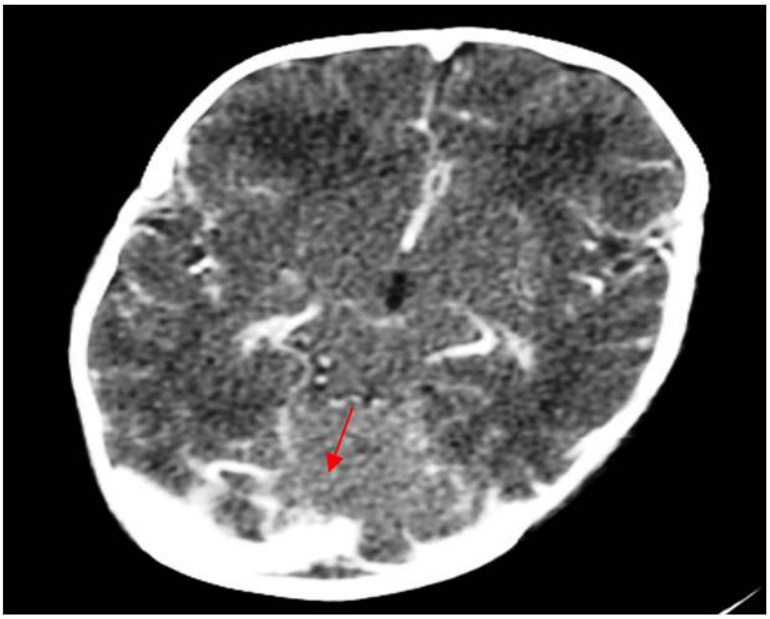

Fig. 1. Brain CT: An infant of 36 week's postconceptional age and IUGR with siezure, slit- like lateral ventricle due to brain edema and tiny hyperdensity in posterior fossa due to cerebral venous sinus thrombosis

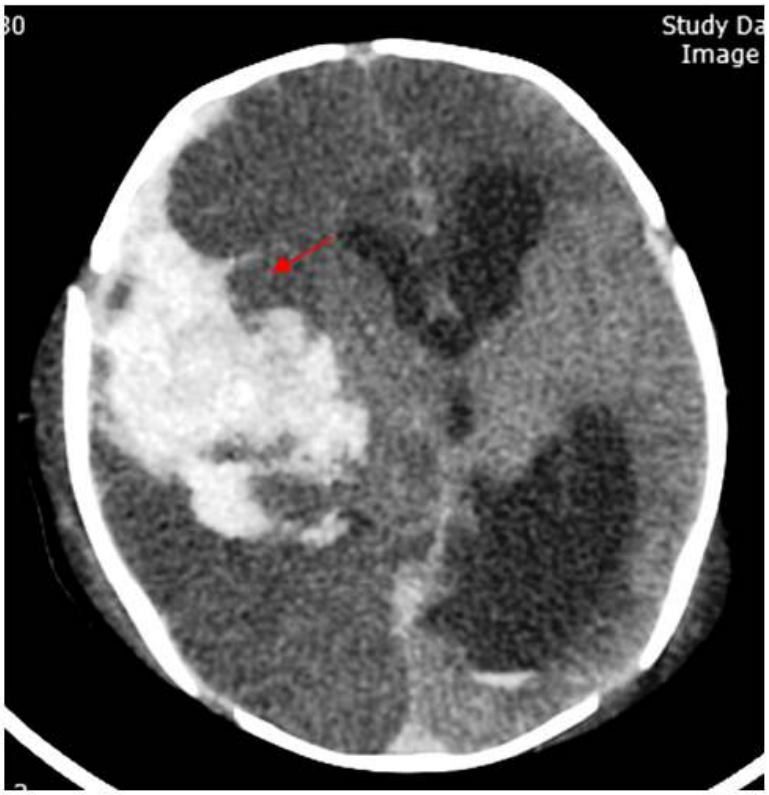

Fig. 2. Brain CT: An infant of 39 week's postconceptional age with siezure, sever ICH with midline shift and left ventriculomegaly and widening af the cranial sutures

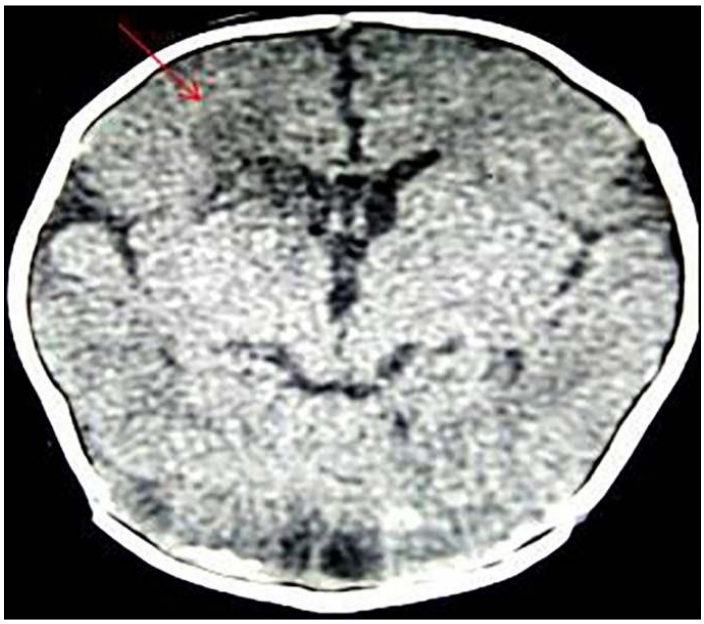

Fig. 3. Brain CT: An infant of 38 week's postconceptional age with meningitis and siezure, low attenuation areas around the right lateral ventricle and at caudate head, which was suggestive of hypoxic ischemic insult

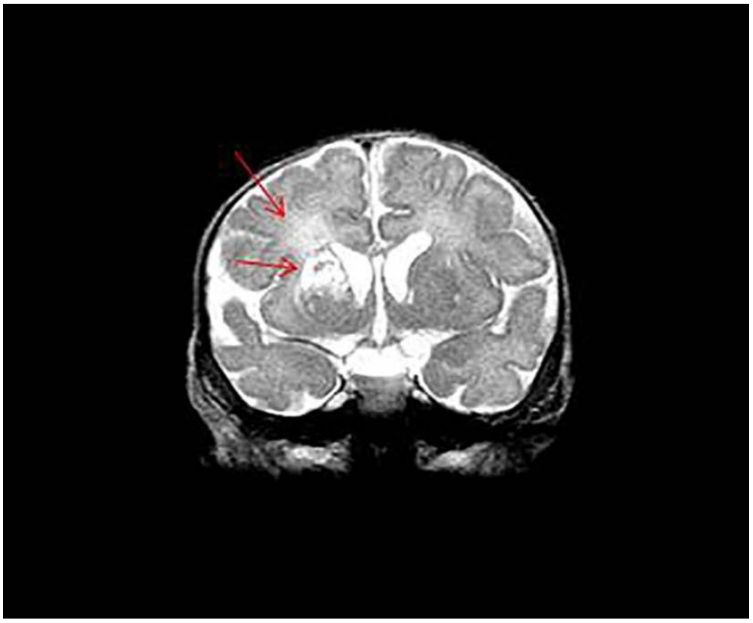

Fig. 3A. Brain MRI: (From the infants Above): Demonstrated bilateral periventricular cyst formation, mainly on the right side of the caudate head and putamen, which represented brain abscess

In this study, of the 20 infants with resistant seizure and lack of seizure control after using the single dose of Phenobarbital and Phenytoin, 17 infants have responded to levetriacetam. Similar results have also been reported by other research. In one such research, of the 144 neonates, who were treated by LEV, 132 of them had no seizure (90% response to treatment) and

in a specific etiology, the response rate to the treatment was 71%(10),which is aligned with our study. However, the slight difference in percentage is due to the difference in etiology, therapeutic dose and sample size. In Furwentsche's study, after 6 days of treatment all the 6 studied neonates were seizure free [23]. This difference can be due to the difference in the definition of seizure control response in time longer than our study. In Abend's study, seizure did not control in 8 of 23 (35%) infants [24], which can be due to the amount of drug dose, method of seizure diagnosis, describing seizure control and method of selecting patients for treatment and differences in etiology. In Rakshasbhuvankar's study, after receiving levetriacetam, there were termination or 80% reduction of seizure in 75% of neonates [25], which is aligned with our study. The slight difference in percentage is, however, due to the selection of premature infants (from gestational age 22 weeks until term) and also etiology and therapeutic dose. In this study, the average patients age is 13±10.5 days (1-29), which is aligned with Kumar's study [26].

Table 3. Comparison of the variables between responder and nonresponder groups

Variable	Responder	Nonresponder	p value
Sex(n)female/male	3/14	0/3	1
Delivery C/S/NVD(n)	13/4	2/1	1
Birth weight(n)			
<2500gr	6	0	0.52
>2500gr	11	3	
F.H of Epilepsy(n)			
Yes	1	1	0.28
No	16	2	
Relative Parents(n)			
Yes	11	1	0.53
No	6	2	
Number of status epilepcticus seizure before LEV(n)			
NL	5	2	
<5	8	1	1.5
>5	4	0	
Abnormal EEG(n)			
Yes	3	12	0.53
No	0	5	
Abnormal neuroimaging(n)			
Yes	15	3	3.1
No	2	0	
Seizure after 24h(n)			
Yes	4	3	0.03**
No	13	0	
Seizure after 72h(n)			
Yes	3	1	0.5
No	14	2	
Mortality(n)			
Yes	2	0	1
No	15	2	
Tracheal intubation(n)			
Yes	4	3	0.03**
No	13	0	

Abbreviations: F.H: Familial History
EEG: Electroencephalogram
LEV: Levetiracetam
***: Significant level (α<0.05)*

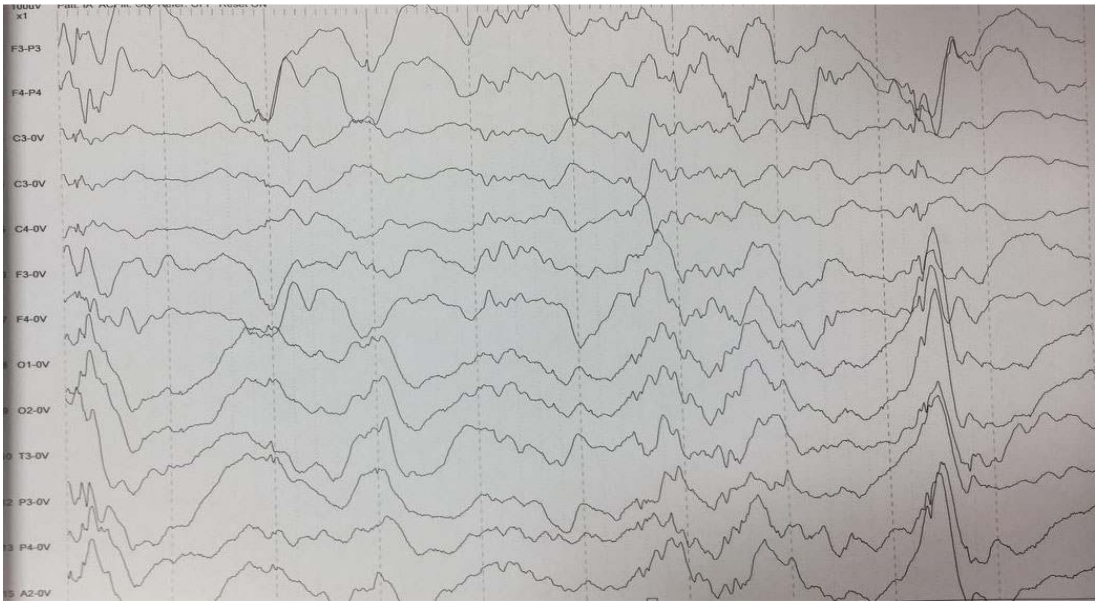

Fig. 4. An infant of 38 week's postconceptional age with hypoxic ischemic encephalopathy and seizures on days 3 of life. some genrelized epileptiform discharge and polyspike waves are seen

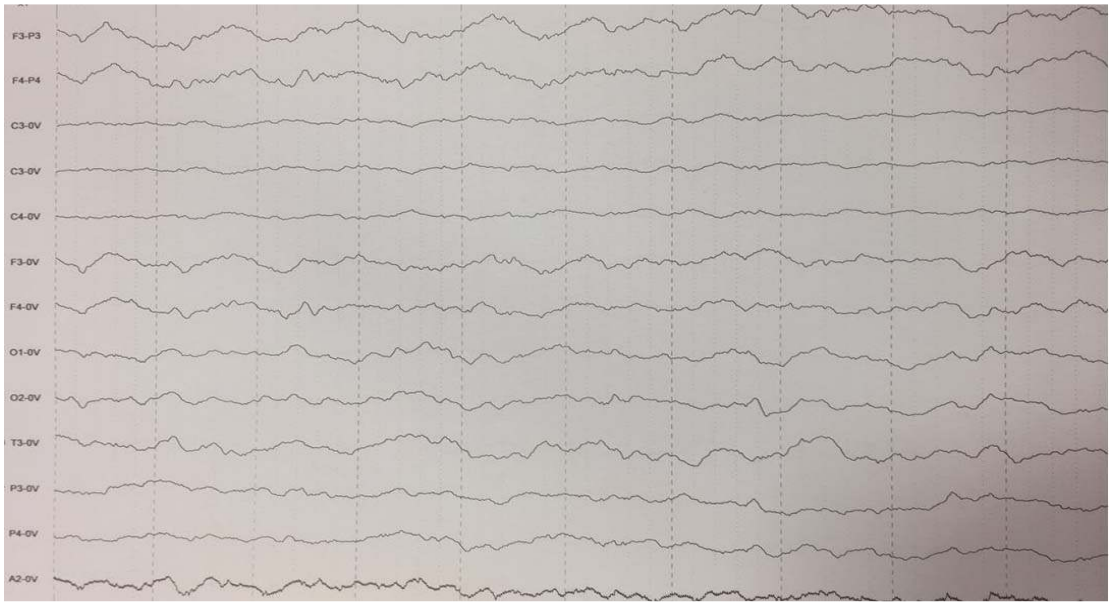

Fig. 4A. From the infant above after treatment with Levetiracetam, normal sleep EEG, active sleep, trace discontinue are seen

In Abend study, the average infants age was 14±13 days, where the difference in study could be explained by the age selection of the infants which in theirs were between 1 to 41 days [24]. 85% of patient were boys like previous studies were done [27]. In another similar study in Barcelona on 77 infants, from which 63.6% were boys [28], the results were, equally, in alliance with ours. In present study, the average gestational age (G.A) was 37.3 ±1.9. Results indicate that the effect of LEV has been more desirable on the G.A of more than 37 weeks (58.8%) rather than less than 37 weeks. Nonetheless, still no meaningful connection is

found between the use of LEV and the G.A.(P>0.05). In Yau's study, the effect of LEV in neonatal seizure with G.A of more than 36 weeks showed more favorable results in treatment of seizure symptoms, which is also aligned with our study [16]. In Reme's study, which has been a prospective cohort multi-centered study on the treatment of seizures in infants, 85% of the candidates were more than 36 weeks in G.A, which may have been caused by the large number of candidates, i.e. 611 from which 519 infants had more than 37 weeks [23]. In this study the most common reasons of seizure were Hypoxic Ischemic Encephalopathy (45%), which is similar to pervious study [16,24,29,30]. In this study 47.1% of the infants with Hypoxic Ischemic Encephalopathy responded to treatment with LEV which is similar to the study of Painter with 50% success rate in controlling seizures [31].

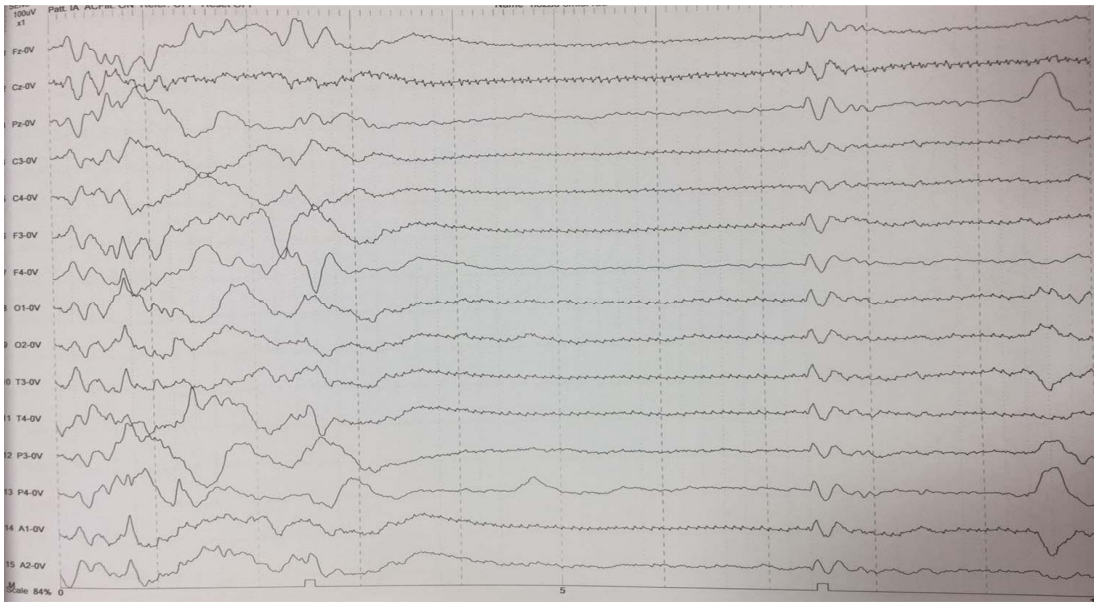

Fig. 5. An infant of 37 week's postconceptional age with moderate hypoxic ischemic encephalopathy with modified suppression burst

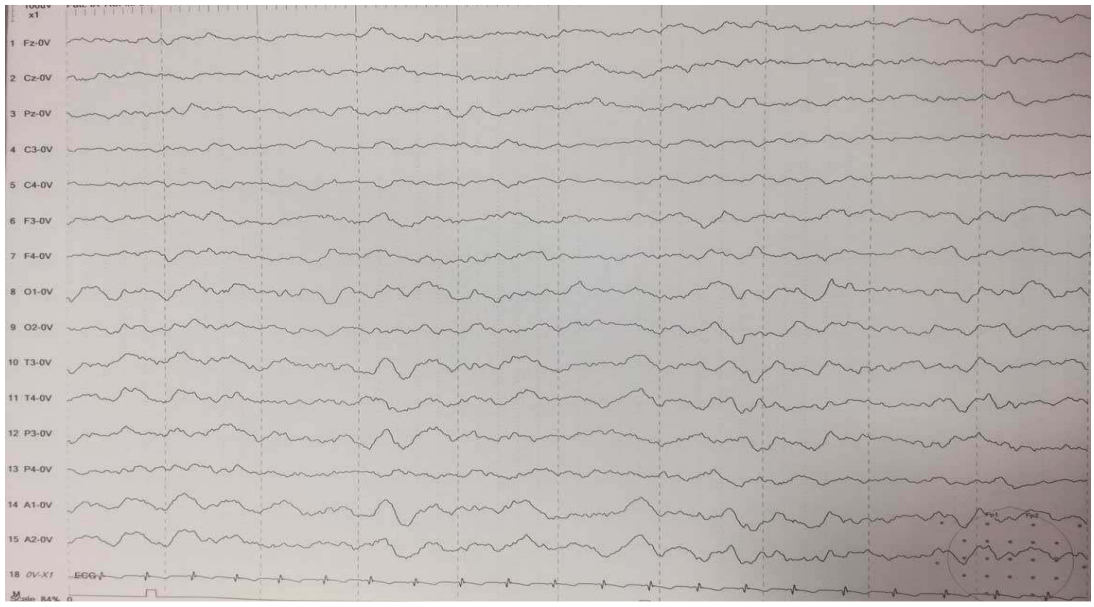

Fig. 5A. From the infant above with normal active sleep after treatment with Levetiracetam

In Sharpe's study in neonates 37-41 weeks with seizure due to hypoxic ischemic encephalopathy had improvement with loading dose of 20 mg/kg and maintenance dose 50 mg/kg/day of LEV in the first week of treatment [32]. In this study of 20 infants none showed side effects of LEV which is similar to previous studies [33-35]. Same results are shown in Furwentsche's study with candidates showing no side effects except one case who suffered mild drowsiness which could have caused by simultaneity use of Phenobarbital [23]. In present study, the loading dose of LEV has been 10-50 mg/kg and the maintenance dose has been 5-30 mg/kg/days which is similar to Ramantani's study with 10-30 mg/kg/days of maintenance dose [36]. The treatment dose of the present study is different from some other recent studies [16,24,29,30], and the reasons for this difference are due to unclear pharmacokinetics of LEV, not having a proper pattern for prescribing the medicine, and also lack of knowledge of the optimal dose in neonates. Of the two mortalities of the present study, one was caused by hypoxic ischemic encephalopathy and another by metabolic disease, which is similar to the two mortalities in the study of Yau and his colleagues [16]. It is also aligned with the study of Abaskhanian and his colleagues of the mortalities in seizure suffering infants [37]. In this study, 76.5% of the infants who responded to the treatment of LEV were not intubated. The 3 other infants who did not respond to the treatment were put on the next anti-epileptic drug, i.e. midazolam, were intubated, which is in line with Yau's studies. Therefore, in case of not using anesthetic drugs، LEV is effective in preventing intubation [16].

In the present study, 13 infants (65%) were seizure free after 24 hours and unexpectedly after 24 hours in infants who continue to have seizure, there were infants who did not respond to levetriacetam and also in 80% of infants, seizure was controlled after 72 hours.

The findings of this research is, to some extent, similar to Yau 's study, in which 58% and 75% of the infants were reported to be seizure free after taking LEV in 24 and 72 hours, respectively [16]. In addition, the findings of the present study are similar to Painter's study, a randomized crossed-over study, which compared the effect of Phenobarbital and Phenytoin in neonatal seizure treatment, which reported that 9 infants (75%) were seizure free in 72 hours after taking LEV. [31]. However, the findings of our research are different from Khan's study, which reported that seizure stopped completely (100%) after 72 hours of using LEV [38]. These differences could be due to several reasons, including: different method in selecting patients (all infants were term and over 37 weeks), different treatment options for patients, using one antiepileptic for 72% of their patients, two antiepileptic for 9% of them and three antiepileptic drugs for 5% of them, and lastly, difference in therapeutic dose and describing the seizure interruption. In the present study, 90% of neuroimaging findings were abnormal, in which 8 out of 20 cases were suffering from hypoxic changes and periventricular leukomalacia as the most common among them (40%). In Lo-Yee's study, 9 infants in neuroimaging were suffering from hypoxic changes, cystic encephalomalacia and periventricular leukomalacia. One infant had hydrocephalus with generalized atrophy and 2 infants had normal neuroimaging, which in the terms of prevalence, Hypoxic changes and cystic encephalomalacia and periventricular leukomalacia were more common than others and was aligned with our study [16]. Similar studies are discussed in Table 4.

The limitations of the present research are as follows: first, the small number of infants admitted to the NICU—i.e. each year nearly 400 infants are admitted of which only 20% of them suffer from seizure. Thus, the sample size was low. Due to the limited number of samples and good response of patients to levetiracetam, there is a significant difference between the number of responders and non-responders. Thus, the possible differences between the LEV responsive and unresponsive group were not really investigable. In addition, given that the first-line treatment of status epilepticus episodes in NICU (the subject hospital of this research) is still phenobarbital and phenytoin, it was risky to start to use levetiracetam as the first-line treatment, which is still off label. To evaluate the effect of levetiracetam and reduce the effects of phenobarbital drowsiness, a loading dose of maximum 20 mg / kg Phenobarbital was used instead of the usual loading dose of maximum 40 mg / kg. Therefore, absolute effectiveness of LEV because of the concomitant use of other anti-epileptic drugs could not be measured reliably. Lack of standard and optimal dose because the pharmacokinetics of drug has not been well distinctive in neonates. Other limitations included not having a control group and not focusing on infants under 30 weeks.

Table 4. Similar studies with this study

Variables	Our study	Other study
Response to LEV	from 20 infants with resistant seizure and lack of seizure control after using the single dose of Phenobarbital and Phenytoin,17 infants have responded to levetriacetam.	**Mruk AL,** 90% response to treatment) and in a specific etiology response rate to treatment was 71% **Rakshasbhuvankar A** after receiving LEV there were termination or 80% reduction of seizure in 75% of neonates
G.A	the mean(G.A) was 37.3 ±1.9. Results indicate that the effect of LEV has been more desirable on the G.A of more than 37 weeks (58.8%) rather than less than 37 weeks.	**Yau ML-Y** G.A of more than infants was 37 weeks (58.8%)
Sex	85% of patient were boys	**Cho JI, Alcover-Bloch E,** on 77 infants, from which 63.6% were boys
Etiology	The most common reasons of seizure were Hypoxic Ischemic Encephalopathy (45%)	**Yau ML-Y, Abend NS ,Khan O ,Ronald G** the most common etiology were HIE
Side effect	On 20 infants none showed side effects of LEV	**Vencatesan C,Shin JW**, **Sedighi M** no side effects of LEV were reported
Dose of LEV	the loading dose of LEV has been 10-50 mg/kg and the maintenance dose has been 5-30 mg/kg/days	**Ramantani G,** maintenance dose was 10-30 mg/kg/days
Mortality	Two mortalities of this studies were caused one by hypoxic ischemic encephalopathy and another by metabolic disease	**Yau ML** The most common cause of mortality were HIE and inborn errors of metabolism
Intubation	76.5% of the infants who responded to the treatment of LEV were not intubated and the 3 infants who did not respond to the treatment were intubated	**Yau ML-Y** LEV was effective preventing intubation
Response to LEV after 24 h and 72 h	65% and 80% of of infants were seizure free after 24 and 72 hours of the treatment	**Yau ML-Y** 58% in 24 hours and 75% after 72 hours were seizure free **Painter MJ** that 9 infants(75%) 72 hours after taking LEV were seizure free
Neuroimaging	90% of neuroimaging findings were abnormal which Hypoxic changes and periventricular leukomalacia as the most common among them (40%)	**Yau ML-Y** Hypoxic changes and cystic encephalomalacia and periventricular leukomalacia were more common
Response to LEV in HIE infants	47.1% of the infants with Hypoxic Ischemic Encephalopathy responded to treatment with LEV	**Painter MJ** 50% success rate in controlling seizures **Sharpe DV** in neonates 37-41weeks with seizure due to HIE had improvement in the first week of treatment

HIE: Hypoxic ischemic encephalopathy

Lastly, in this study, infants were not followed-up and the study was only conducted during the hospitalization. Thus, future studies are suggested to have follow-up.

5. CONCLUSION

The present study benefited from the inclusion of many variables that made this study similar and equally different from the previous research on the subject. We used new variables, which were less or not examined in previous research. One such variables was the reduced risk of intubation in neonates responding to Levetiracetam. Given that LEV is a newly used medication in neonates, the multiplicity of valuable variables used in the present research adds to the significance of this study.

Using of video-EEG has helped in improving the study. According to the results of this study, like those of the previous research, LEV can be effective as a second-line therapy in the treatment of resistant neonatal seizure and in reduced seizure in hypoxic ischemic encephalopathy. For a better understanding of LEV's effects in the treatment of intractable seizure in neonates, it is better to check with the large samples and multi-centered and done as clinical trial. In addition, the optimal and standard dose can be examined in future research.

CONSENT

As per international standard or university standard, patient's written consent has been collected and preserved by the authors.

ETHICAL APPROVAL

As per international standard or university standard, written approval of Ethics committee has been collected and preserved by the authors.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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