Original Article

Response of Add-On Oral Levetiracetam in Neonates Having Refractory Seizure

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ABSTRACT

Objective: To evaluate the efficacy of add on oral levetiracetam in neonates having refractory seizure.
Study Design: A prospective clinical trial
Place and Duration of the Study: This study was conducted at the Department of Pediatrics, Services Hospital, Lahore from June 2018 to March 2019.
Materials and Methods: We analyzed 60 neonates visiting neonatal emergency with seizure, who did not respond to initial intravenous (IV) phenobarbital or subsequent addition of IV phenytoin. We went on to use oral levetiracetam as an add on therapy. Oral levetiracetam as gavage as a starting dose of 10 to 20 mg per kg and gradual increase to 40 to 50 mg per kg if a repeat of seizure occurred according to clinical signs and then, persistence or complete control of seizure was monitored. Chi square test was applied to the effect of study variables on the response of levetiracetam and p value < 0.05 was considered as statistically significant.
Results: Out of a total of 60 neonates, most were 40 (66.7%) male, had gestational age status as term 38 (43.3%), delivered by cesarean section (CS) 39 (65.0%), aged less than or equal to 7 days 42 (70.0%). Tonic seizure was found to be the most frequent type, in 19 (31.7%) while 18 (30.0%) had idiopathic as the commonest underlying cause of seizure. There were 56 (93.3%) neonates who went on to positively respond to add on therapy of oral levetiracetam.
Conclusion: Oral levetiracetam as an add on therapy was found to have excellent response in neonate having seizure after the failure of 1st line treatment options.

Key Words: Neonatal Seizure, Levetiracetam, Idiopathic, Response.

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INTRODUCTION

Seizure is described as sudden alteration in behavior, sensory or autonomic function which are related to dysfunction of paroxysmal electrical activity of brain.[1-3]Noenates are said to be affected more in comparison to children of any other age, estimating about 1 to 5 per 1000 live births.[4,5] In children, variation persists in reported prevalence of seizures due to difference in definitions and well as challenges in timely diagnosis but still a yearly prevalence of around 1% is noted around the world.[6,7] Neonatal seizure is noted to be one of the most frequent cause of admissions while the pattern of disease vary greatly.[8]

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In neonates, seizures are classified in to various types like subtle, clonic, tonic, spastic as well as myoclonic.[9,10]Asphyxia as well as hypoxic-ischemic encephalopathy (HIE) are known to be the most common causes of seizure in neonates, accounting 50% to 75% of cases. Infectious diseases, metabolic disorders, injuries, intracranial hemorrhages and abnormalities related to structure of the brain are some of the other known causes of seizures in neonates.[11,12]
It has also been noted commonly that central nervous system (CNS) premature neonates exhibit non-specific response. Most seizures involving neonates have good outcome while some may go on to develop complications of transient or chronic nature.[13] The brain is noted to develop in the first few years that is why frequent seizure can alter the development as well as learning potential due to structural changes related to brain.[6] That is why it is imperative to aim inhibition of seizures by adopting efficacious drugs.
Lots of antiepileptic options are available to tackle seizures, mainly depending upon the etiological factors suspected.[14]Phenobarbital followed by phenytoin are considered to be the 1st line treatment options for neonatal seizure.[6] Phenobarbital accompanies powerful anticonvulsive benefits but low toxicity that is why WHO holds it as 1st line treatment option for generalized, tonic, clonic and partial seizures.[15,16]

It has also been noticed that around 40% of seizures do not respond with either phenobarbital and phenytoin that presents a space for the addition of other anti-convulsive drugs.[17,18]Topiramate, levetiracetam and lamotrigine are some of the newer recommended antiepileptic options available for the treatment of neonatal seizure. Levetiracetam as an add on therapy has been studied recently and was found to yield good result as 1st line add on therapy.[19] Levetiracetam has a non-hepatic metabolism and addition of no drug interaction without any major complications or neurotoxic effects[20,21] makes it a valuable to choice to test in our local population. To shed more light on this new drug, we planned this study to evaluate the efficacy of add on oral levetiracetam in neonates having refractory seizure.

MATERIALS AND METHODS

This prospective clinical trial was conducted at The Department of Pediatrics, Services Hospital, Lahore, from 1st June 2018 to 31stMarch 2019. We analyzed all neonates visiting neonatal emergency withseizure were enrolled. Inclusion criteria was all those neonates who did not respond to initial intravenous phenobarbital or subsequent addition of intravenous phenytoin, and were went on to have oral levetiracetam as an add on therapy for refractory seizure. Finally, 60 neonates having refractory seizure met the inclusion criteria and were included in the study while neonates with electrolyte imbalance, presenting with hypoglycemia or not meeting the inclusion criteria, were excluded.

Informed consent was sought from parents / guardians of all the study participants. Approval from institutional Ethical and Research Committee was granted.

Oral levetiracetam as gavage as a starting dose of 10 to 20 mg per kg and gradual increase to 40 to 50 mg per kg[19] if a repeat of seizure occurred according to clinical signs and then, persistence or complete control of seizure was monitored.

Age, gender, types of delivery, gestational age, type and causes of seizures along with response of levetiracetam was noted in control of seizure in all the neonates. SPSS version 21 was used for data analysis. All the qualitative variables like gender, types of delivery, types and causes of seizure were presented as frequencies and percentages while quantitative variables like age were presented in the form of mean and standard deviation. Chi square test was applied to the effect of study variables on the response of levetiracetam and p value < 0.05 was considered as statistically significant.

RESULTS

Out of a total of 60 neonates, there were 40 (66.7%) male and 20 (33.3%) female. According to the gestational age of neonates, 22 (36.7%) were preterm and 38 (43.3%) term.

Table No.1: Distribution of Response of LevetiracetamandCharacterestics of Neonates

Characteristics		Response to Levetiracetam (n=60)			P Value
		Positive Response (n=50)	No Response (n=4)	Positive Response by Increasing Dose (n=6)	
Gender	Male	32 (64.0%)	2 (50.0%)	4 (66.7%)	0.842
	Female	18 (36.0%)	2 (50.0%)	2 (33.3%)	
Preterm (<37 weeks)		20 (40.0%)	1 (25.0%)	1 (16.7%)	0.471
Term (>37 weeks)		30 (60.0%)	3 (75.0%)	5 (83.3%)	
Type of Delivery	NVD	18	1 (25.0%0	2 (33.3%)	
	CS	32	3 (75.0%)	4 (66.7%)	
Postnatal Age (days)	<7	36 (72.0%)	3 (75.0%)	3 (50.0%)	0.152
	8-14	2 (4.0%)	1 (25.0%)	2 (33.3%)	
	15-21	5 (10.0%)	0 (0%)	1 (16.7%)	
	22-28	7 (14.0%)	0 (0%)	0 (0%)	
CNS Infection	Yes	1 (2.0%)	0 (0%)	1 (16.7%)	0.155
	No	49 (98.0%)	4 (100%)	4 (13.3%)	
Type of Seizure	Tonic	14 (28.0%)	3 (75.0%)	2 (33.3%)	0.630
	Subtle	5 (10.0%)	0 (0%)	1 (16.7%)	
	Spastic	13 (26.0%)	0 (0%)	1 (16.7%)	
	Clonic	7 (14.0%)	0 (0%)	0 (0%)	
	Mixed	11 (22.0%)	1 (25.0%)	2 (33.3%)	
Underlying Disease					
HIE		14 (28.0%)	0 (0%)	2 (33.3%)	0.264
Brain Malformation		9 (18.0%)	2 (50.0%)	0 (0%)	
IEM		7 (14.0%)	2 (50.0%	2 (33.3%)	
IVH		4 (8.0%)	0 (0%)	0 (0%)	
Idiopathic		16 (32.0%)	0 (0%)	2 (33.3%)	

There were 39 (65.0%) neonates who were delivered by cesarean section (CS) while 21 (35.0%) by normal vaginal delivery (NVD). Majority, 42 (70.0%) of the neonates were aged less than or equal to 7days. Only 2 (3.3%) neonates were found to have CNS infection. Tonic seizure was found to be the most frequent, in 19 (31.7%) neonates while spastic 14 (23.3%), 6 (10.0%) subtle, 7 (11.7%) clonic and mixed form was noted in 14 (23.3%). In terms of underlying causes of seizure in studied neonates, 18 (30.0%) were idiopathic, 16 (26.7%) had HIE, 11 (18.3%) brain malformation, 11 (18.3%) inborn errors of metabolism (IEM) and 4 (6.7%)intraventricular hemorrhage(IVH).

In terms of response of levetiracetam, 50 (83.3%) neonates were noted to have positive response (complete control of seizures) while 6 (10.0%) more achieved complete cessation of seizure with increase in dosage of oral levetiracetam, whereas 4 (6.7%) neonates did not respond to the studied treatment.

When neonates having positive response to levetiracetam, with no response and response by increasing the dosage were compared within different study variables, no significance was found in terms of response ($p > 0.05$). We did not notice any side effects related to oral levetiracetam.

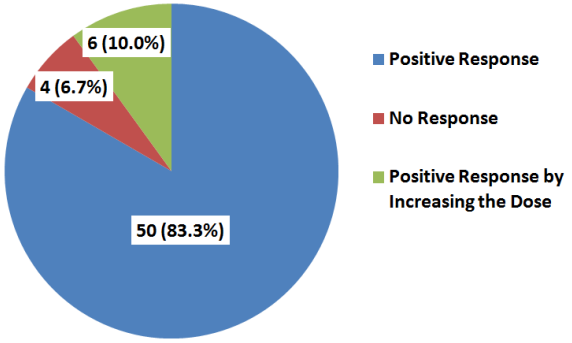

Figure No.1: Response of Levetiracetam Amongst All the Neonates

DISCUSSION

In the current study, we included those neonates who did not respond to 1st line treatment options. We noticed that a total of56 (93.3%) neonates went on to positively respond to add on therapy oforal levetiracetam while only 4 (6.7%) did not respond at all, even after increasing the dosage. Not much work has been done in the recent past to evaluate the effectiveness of levetiracetam in neonates presenting with seizures. This study was aimed to evaluate the newer options like levetiracetam to help clinicians picking up effective and modern option while facing seizures in neonates. No real work was found specifically analyzing oral levetiracetam so the result of this study will surly add to the little knowledge that currently exist in this regards The results of the present study in terms of positive response are very consistent to a study conducted by Mollamohammadi M et al in Iran[19] also analyzed the response of oral levetiracetam in 42neonates with seizures, found an overall positive response of 95%.

Levetiracetam has been studied well in IV form for control of seizure in neonates. A study analyzing 38 neonates,[22] IV levetiracetam was administered as 1st line therapy in comparison to IV phenobarbital and the results proved that IV levetiracetam turned out to have better efficacy for the control of neonatal seizures versus IV phenobarbital.In another study conducted by Khan O and colleagues,[23] IV levetiracetam was used in a dosage of 10-50 mg/kg, and was found to subside seizure in all neonates while all of them got discharged on oral levetiracetam.

In the present study, we did not notice any significant relationship between levetiracetam response rate and any of the studied variables. Our findings in these aspects were very similar to what has been found earlier as well. We did not notice any side effects related to oral levetiracetam which is very consistent with the previous findings.[19]

CONCLUSION

Oral levetiracetam as an add on therapy was found to have excellent response in neonate having seizure after the failure of 1st line treatment options. Further studies having bigger sample size assessing the response of various forms of levetiracetam are needed to authenticate the findings of the current research that will be hugely beneficial for the treatment of seizure in neonates.

Author's Contribution:

Concept & Design of Study:	Farhan Zahoor
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Conflict of Interest: The study has no conflict of interest to declare by any author.

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