Original Article

Effectiveness of Levetiracetam as a First Line Anticonvulsant for Neonatal Seizures

Muhammad Hayat Khan, Syeda Shireen Gul, Qaiser Zaman, Nadeem Ahmad and Qurrat-ul-Ann

ABSTRACT

Objective: To determine the effectiveness of levetiracetam as a first line anticonvulsant in neonates presenting with seizures at a tertiary care hospital.

Study Design: Prospective study.

Place and Duration of Study: This study was conducted at the Department of Neonatology, Pakistan Institute of Medical Sciences (PIMS) Hospital, Islamabad from 23rd December, 2020 to 22nd June, 2021.

Materials and Methods: One hundred and thirty eight neonates having clinical seizures with and without having documented EEG abnormality were enrolled. Levetiracetam as 50 mg/kg loading dose (diluted in 20 ml normal saline) was administered intravenously in 20 minutes, followed by a maintenance dose of 20 mg/kg intravenously every 12 hours. An additional 20 mg/kg loading dose of levetiracetam was administrated in case of persistent seizures despite initial levetiracetam load. Response to the levetiracetam was considered as the cessation of seizures clinically within a time frame of 30 minutes.

Results: There were 79 (57.2%) males. Overall, mean age was 6.27±6.5 days. Mean birth weight was 2.33±0.64 kg. There were 80 (58.0%) neonates who belonged to urban areas of residence. There were 42 (30.4%) neonates who were born pre-term. Lower segment cesarean section was the commonest mode of delivery noted among 70 (50.7%) cases. Most frequent etiology of seizures was found to be sepsis 57 (41.3%) while hypoxic ischemic encephalopathy was reported in 49 (35.3%). Levetiracetam treatment was found to be successful in 122 (88.4%) neonates. No drug related serious adverse events were reported.

Conclusion: Levetiracetam was found to be highly effective as a first line anticonvulsant in neonates presenting with seizures. No drug related serious adverse events were observed.

Key Words: Levetiracetam, Anticonvulsant, Neonate, Seizures

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INTRODUCTION

Seizure in neonates is a common medical emergency. The incidence of seizures in estimated to be more in pre-term newborns (ranging between 0.6-5/1000 live-births).[1] Most commonly observed etiologies of neonatal seizures are hypoxic-ischemic encephalopathy, congenital malformations, infection, intracranial hemorrhage, thrombosis and inborn metabolic disorders.[2]

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Neonatal seizures are considered to be an important cause of neurological impairments, delay and it is associated with increased risk of neonatal mortality.[3]

Data from developed countries show that there are controversies regarding optimal management options for neonatal seizures.[4,5] In the past, phenobarbital followed by phynytoin or fosphenytoin have been the mainstay of treatment in neonatal seizures.[6]Currently FDA approved anti-epileptic options including phenobarbital and phenytoin exhibit efficacy in less than half of the neonates suffering with seizures while adverse events related with these drugs also common.[7,8] Levetiracetam has a unique mode of action where it binds to unique site. Levetiracetam has rapid absorption, renal excretion and has not been reported to modulate Na, K or Ca channels while no cardiotoxicity has been reported with its therapeutic dosages.[9]Due to these benefits, levetiracetam can be preferred over its contemporary drugs.[10]A study by Kreimer et al[11]reported seizures control in 47% patients using levetiracetam monotherapy.

While a study by Falsaperla et al[12] reported that levetiracetammono-therapy is effective in 100% patients for the treatment of seizures. While another study by Ragunathan and Chandrasekhar[13] reported seizures control in 64.7% patients presenting with seizures using levetiracetam monotherapy. The aim of the present study is to determine the effectiveness of levetiracetam as 1st line anticonvulsant in neonates presenting with seizure at a tertiary care hospital. The findings of this study were thought to help to determine the success rate of levetiracetam for seizures control in our local population.

MATERIALS AND METHODS

This prospective study was conducted at Department of Neonatology, Pakistan Institute of Medical Sciences (PIMS) Hospital Islamabad from23rd December, 2020 to 22ndJune, 2021, and comprised 138 neonates. Inclusion criteria was neonates having clinical seizures (focal/ generalized clonic/tonic, myoclonic, subtle) with and without having documented EEG abnormality. Neonates having prior treatment with antiepileptic drugs other than benzodiazepines, were excluded.

After inclusion of the neonates, levetiracetam as 50 mg/kg loading dose (diluted in 20 ml normal saline) was administered intravenously in 20 minutes, followed by a maintenance dose of 20 mg/kg intravenously every 12 hours. An additional 20 mg/kg loading dose of levetiracetam was administrated in case of persistent seizures despite initial levetiracetam load. Response to the levetiracetam was considered as the cessation of seizures clinically within a time frame of 30 minutes from the initiation of the intravenous drug therapy. If the seizures did not stop within 30 minutes after starting the infusion, additional 20 mg/kg loading dose of levetiracetam was administrated. Cessation of seizures as observed clinically within this additional time frame was also considered as the response to the drug. If the seizure episode did not cease within the total time frame of 60 minutes, it was considered as treatment failure. In failed cases, intravenous phenytoin (20 mg/kg diluted in 20 ml of normal saline) was administered. All the study relevant information was noted. The collected information was analyzed with SPSS version 26. P value ≤0.05 was considered as significant.

RESULTS

There were 79 (57.2%) male. Overall, mean age was 6.27±6.5 days (ranging between 1 to 28 days). Mean birth weight was 2.33±0.64 kg (ranging between 1kg to 3.5kg). There were 80 (58.0%) neonates who belonged to urban areas of residence. There were 42 (30.4%) neonates who were born pre-term. Lower segment cesarean section was the commonest mode of delivery noted among 70 (50.7%) cases. Most frequent etiology of seizures was found to be sepsis 57 (41.3%) while hypoxic ischemic encephalopathy was reported in 49 (35.3%) [Table 1].

Figure 1 showing effectiveness of levetiracetam in the neonatal seizures and it was noted that levetiracetam was successful in 122 (88.4%) neonates. No drug related serious adverse events were reported.

Table No.1: Demographic information of the neonates (n=138)

Variable	No.	%
Gender		
Male	79	57.2
Female	59	42.8
Age (days)		
≤7	108	78.3
>7	40	21.7
Birth weight (kg)		
<2.5	62	44.9
≥2.5	76	55.1
Area of residence		
Urban	80	58.0
Rural	58	42.0
Gestational maturity		
Term	96	69.6
Pre-term	42	30.4
Gravidity status		
Primigravida	53	38.4
Multigravida	85	61.6
Mode of delivery		
Normal vaginal delivery	68	49.3
Cesarean section	70	50.7
Gestational diabetes mellitus	6	4.3
Eclampsia	17	12.3
Birth asphyxia	53	38.4
Etiology of seizures		
Idiopathic	11	8.0
Hypoxic ischemic encephalopathy	49	35.3
Metabolic	15	10.9
Sepsis	57	41.3
Hemorrhage/thrombosis	3	2.2
Meconium aspiration syndrome	3	2.2

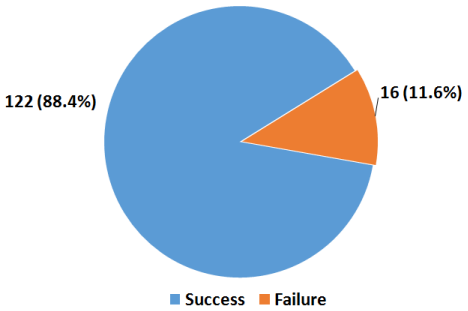

Figure No. 1: Effectiveness of levetiracetam in neonatal seizures

No significant association was found among study variables and treatment effectiveness (p>0.05) except mode of delivery as normal vaginal delivery where 75.0% neonates with failure of treatment had normal vaginal delivery in comparison to 45.9% who had successful outcomes (p=0.029) [Table 2].

Table No.2: Stratification of neonatal characteristics with respect to treatment effectiveness (n=138)

Characteristics of Neonates	Treatment effectiveness		P value
	Success (n=122)	Failure (n=16)	
Male gender	72 (59.0%)	7 (43.8%)	0.246
Age ≤7 days	98 (80.3%)	10 (62.5%)	0.104
Birth Weight <2.5 kg	57 (46.7%)	5 (31.2%)	0.242
Rural Area of Residence	53 (43.4%)	5 (31.2%)	0.353
Pre-Term	40 (32.8)	2 (12.5%)	0.097
Primigravida	50 (41.0%)	3 (18.8%)	0.086
Mode of delivery as normal vaginal delivery	56 (45.9%)	12 (75.0%)	0.029
Gestational diabetes mellitus	5 (4.1%)	1 (6.3%)	0.691
Eclampsia	16 (13.1%)	1 (6.3%)	0.432
Birth asphyxia	49 (40.2%)	4 (25.0%)	0.241
Etiology of seizures			
Idiopathic	11 (9.0%)	-	0.634
Hypoxic ischemic encephalopathy	47 (38.5%)	2 (12.5%)	
Metabolic	15 (12.3%)	-	
Sepsis	52 (42.6%)	5 (31.2%)	
Hemorrhage/Thrombosis	3 (2.5%)	-	
Meconium aspiration syndrome	3 (2.5%)	-	

DISCUSSION

Commonly adopted anticonvulsant options like phenytoin have a relatively low efficacy while adverse events related to phenytoin are also common.[14] Newer antiepileptic treatments are being proposed by the researchers but the data is only limited to case reports and case series.[15,16]Intravenous levetiracetam has become a common 2nd line anticonvulsant choice among pediatric population but evidence about its effectiveness is not abundant.Levetiracetam is a broad-spectrum anti-epileptic agent having approval of usage for seizure prophylaxis in both focal and generalized sizures.[9,10]Intravenous levetiracetam is widely available for those cases who cannot intake oral form.

In this study, we found that levetiracetam had successful treatment outcome in 88.4% neonates while 11.6% did not respond to levetiracetam treatment. These findings are very similar to a study conducted by Reiter et al[16] assessing IV levetiracetam in the management of acute seizures in children who showed that 89% of children remained seizure-free at 1 hour.A study done by Venkatesan et al[17], evaluating 127 neonates who developed seizures after being diagnosed with hypoxic ischemic encephalopathy, found that levetiracetam was effective as either initial or following phenobarbital in 84% neonates while phenobarbital as initial therapy was successful in 61% cases.Levetiracetam is easy to administer and can be given as a five minute infusion into a peripheral IV cannula without the increased risk of serious adverse events (including hypotension, cardiac arrhythmias, extravasation or death). Furthermore, levetiracetam is compatible with both dextrose and normal saline infusion and has limited drug interactions. A study done by McTague et al[18] from UK revealed that intravenous levetiracetam was effective in 81% children having repeated seizures and status epilepticus. Levetiracetam was also found to be safe in the same study.

Our study had some limitations as well. As this was a single center study with a relatively small sample size, the findings of this study cannot be generalized. As we did not have any comparator or control group in this study, further studies should be conducted having randomized controlled design to judge the efficacy of levetiracetam with other available anticonvulsants. We only evaluated immediate outcome of levetiracetam in the present study so studies aiming to evaluate long-term outcomes should also be conducted.

CONCLUSION

Levetiracetam was found to be highly effective as first line anticonvulsant in neonates presenting with seizures. No drug related serious adverse events were observed. Further research should be conducted having randomized controlled design to judge the efficacy of levetiracetam with other available anticonvulsants in the local population.

Author's Contribution:

Concept & Design of Study:	Muhammad Hayat Khan
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Final Approval of version:	Muhammad Hayat Khan

Conflict of Interest: The study has no conflict of interest to declare by any author.

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