World Journal of Advanced Research and Reviews
eISSN: 2581-9615 CODEN (USA): WJARAI
Cross Ref DOI: 10.30574/wjarr
Journal homepage: https://wjarr.com/

(RESEARCH ARTICLE)

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Assessment of knowledge and practice of pediatric residents towards using and efficacy of levetiracetam as treatment for neonatal seizure

Naela Mohammed Musa [1], Ibrahim Adlan [2], Omer Saeed Magzoub [3,*] and Rasha Sidahmed Elhassan Omer [4]

[1] *Specialist General Pediatrician, Sudan.*
[2] *Associated Professor of Pediatric and Child Health, National University, Sudan.*
[3] *Specialist General Pediatrician, Ain Al-Khaleej Hospital, UAE.*
[4] *Assistant Professor of Pediatric and Child Health, Ribat University, Sudan.*

World Journal of Advanced Research and Reviews, 2025, 25(02), 814-821

Publication history: Received on 25 December 2024; revised on 01 February 2025; accepted on 04 February 2025

Article DOI: https://doi.org/10.30574/wjarr.2025.25.2.0370

Abstract

Background: Seizures are a common neurologic complication in neonates, with severity ranging from mild to life-threatening. Despite their prevalence, clinical management guidelines are lacking. Levetiracetam has demonstrated efficacy and safety in older patients, which has spurred interest in its use for neonates. The awareness and understanding of antiepileptic drugs by physicians are crucial for effective management.

Aim: This study aims to evaluate the knowledge and practices of pediatric residents regarding the use of Levetiracetam in treating neonatal seizures.

Methods: We conducted a cross-sectional study involving 257 pediatric residents in Khartoum state from January to May 2021. Participants completed an online Google Form questionnaire, which included questions about their data, current practices in treating neonatal seizures, their use of Levetiracetam, and their knowledge of this drug.

Results: Of the 257 pediatric residents surveyed, 178 (69.3%) were females and 79 (30.7%) were males. The majority were aged 20-30 years (n=128; 49.8%) and were in their fourth year of residency (n=108; 42%). Nearly all participants (n=255; 99.2%) had observed or managed neonatal seizures. Most residents (n=193; 75.1%) used phenytoin as their first-line treatment for neonatal seizures. A total of 201 (78.2%) reported using Levetiracetam for treating neonatal seizures, often in combination with phenytoin (n=65; 25.3%) or phenobarbitone (n=60; 23.4%). Regarding Levetiracetam, 164 (63.8%) residents felt it had a slow onset and took time to stop seizures. Most participants (n=158; 61%) had poor knowledge of Levetiracetam. Common gaps included understanding its protein binding (65%), mechanism of action (68.5%), and indications (80.2%). Better knowledge levels were associated with male residents (P=0.024), those older than 40 years (P=0.037), residents in their third or fourth year (P=0.000), and those working in tertiary hospitals (P=0.042).

Conclusion: Most residents used phenytoin as their primary treatment for neonatal seizures and frequently combined it with Levetiracetam, often alongside phenobarbitone. Despite this, respondents generally had poor knowledge of Levetiracetam. Better knowledge was linked to being male, older age, advanced residency level, and working in tertiary hospitals.

Keywords: Knowledge; Practice; Pediatrics Residents; Levetiracetam; Neonatal Seizure

* Corresponding author: Omer Saeed Magzoub.

1. Introduction

Neonatal convulsions represent a common neurological emergency requiring prompt intervention due to their potential to harm the brain. They arise from sudden, paroxysmal depolarization of neuron groups, resulting in transient changes in neurological function. These seizures frequently signal serious underlying conditions, necessitating targeted treatment to prevent lasting brain damage from repeated episodes [1]. Neonatal seizures are the most common neurological events in newborns, often indicating a variety of central nervous system (CNS) disorders occurring before, during, or after birth. Seizures are more frequent in the neonatal period than at any other stage of life, affecting around 1.5–3.5 per 1,000 full-term infants and 10–130 per 1,000 preterm infants [2].

There is a notable trend indicating a higher seizure risk in preterm infants compared to their full-term counterparts. Prolonged seizures have been linked to adverse neurodevelopmental outcomes [2,3,4], Phenobarbital (PB) has historically been the first-line treatment for neonatal seizures, despite its limited efficacy (~50%) and altered pharmacodynamics in neonates. There is no consensus on second-line therapies, with options like phenytoin, benzodiazepines, levetiracetam (LEV), and lidocaine being considered. Although efficacy and safety data for PB are limited, it remains widely used, while the choice of second-line anti-seizure drugs varies and lacks robust scientific support. Effective treatment is crucial to reduce the risk of long-term neurological impairments [5,6].

Phenobarbital is the most commonly used anti-epileptic drug and is frequently administered as a first-line treatment. However, clinical control of neonatal seizures with phenobarbital and phenytoin is achieved in only 50–70% of newborns, with even lower effectiveness in cases of neonatal electrical seizures. Moreover, there are concerns regarding short-term side effects, potential neurodevelopmental abnormalities, and drug interactions [7,8]. Levetiracetam (LEV) is a broad-spectrum anti-seizure medication (ASM) with favorable pharmacokinetics and tolerability. It exerts its effects by binding to synaptic vesicle glycoprotein 2A (SV2A), modulating calcium-dependent neurotransmitter release, and reducing vesicle exocytosis. However, the exact mechanism behind its antiepileptic effects is not fully understood [9,10,11]. Due to its promising side effect profile and pharmacokinetics and positive efficacy outcomes in neonatal studies, LEV has garnered significant interest in the treatment of neonatal seizures [12].

Physicians' understanding of seizure definitions, including distinctions between simple and complex seizures, and their treatment approaches significantly influence management decisions. Variability exists in how seizures are managed among residents, physicians, and consultants, even within the same specialty. Given the promising outcomes associated with LEV and its complication-free use, this study aims to evaluate the variability in neonatal seizure management and assess pediatric residency doctors' knowledge regarding the use of Levetiracetam in treating neonatal seizures.

2. Methodology

This descriptive cross-sectional study was conducted at the Sudan Medical Specialization Board (SMSB) from January to June 2021. Established by presidential decree in 1995 under the Sudan Medical Specialization Act, SMSB is the sole institution in Sudan responsible for managing and delivering medical and health specialty training. Its specialty councils oversee all training activities, including curriculum development and review. The study focused on residents who were members of the Council of Pediatrics and Child Health within SMSB. Residents who agreed to participate and Residents working in hospitals located within Khartoum State were included and residents who declined to participate were excluded. The required sample size was calculated using Thompson's equation, resulting in a total of 257 participants. Data were collected using an online Google Forms questionnaire. The questionnaire included sections on personal information, current practices for treating neonatal seizures, the use of Levetiracetam, and knowledge about Levetiracetam.

2.1. Levels of Care

- Primary Hospital: Basic care provided by general practitioners or family physicians.
- Secondary Hospital: Intermediate care provided by medical specialists and other health professionals.
- Tertiary Hospital: Highly specialized consultative care.

2.2. Knowledge Assessment:

Knowledge about Levetiracetam was assessed through eight questions using a Likert scale. Responses were scored as "1" for correct answers and "0" for incorrect ones. A score above 50% (more than 4 correct responses) was considered indicative of good knowledge.

2.3. Study Variables

- Independent Variables: age, gender, years of residency, and level of care.
- Dependent Variables: Treatment practices for neonatal seizures, including the use of Levetiracetam and knowledge about Levetiracetam.

2.4. Data Analysis

Data were analyzed using the Statistical Package for Social Sciences (SPSS) Version 21.0 and presented in tables and figures created with Microsoft Excel 2010. The Chi-Square test was used to determine statistical significance, with a p-value of 0.05 considered significant.

3. Results

The study included 257 resident doctors, of whom 178 (69.3%) were female and 79 (30.7%) were male. Most participants were aged between 20 and 30 years (n=128; 49.8%) and were in their fourth year of residency (n=108; 42%). Over half of the participants (n=147; 57.2%) worked in secondary-level hospitals [Table 1].

Nearly all residents (n=255; 99.2%) had experience managing neonatal seizures. The primary causes identified were hypoxic-ischemic encephalopathy (n=252; 98.1%), meningitis (n=222; 86.4%), and septicemia (n=196; 76.3%), each affecting more than 75% of the cases. Phenytoin was the most used first-line treatment for neonatal seizures, administered by most participants (n=193; 75.1%). This was followed by Phenobarbitone (n=49; 19.1%), Benzodiazepines (n=9; 3.5%), and Levetiracetam (n=6; 2.3%). Most residents (n=241; 94%) reported that seizures resolved with medication [Table 2].

Regarding Levetiracetam, 201 (78.2%) participants used it to treat neonatal seizures, often in combination with other medications such as Phenytoin (n=65; 25.3%) and Phenobarbitone (n=60; 23.4%) [Table 3]. Reactions to Levetiracetam varied: 164 (63.8%) noted a slow onset, 35 (13.6%) observed immediate cessation of seizures, and 2 (0.8%) reported no response. Many respondents (n=91; 35.4%) noted that the drug took between 1 and 6 hours to show effects. Additionally, 77 (30%) residents reported that Levetiracetam was available in their hospital. Knowledge of Levetiracetam varied among participants: most (n=247; 96.1%) had heard of the drug, 214 (83.3%) knew it was used as an anticonvulsant for neonatal seizures, and 213 (82.9%) were aware that it could be administered to neonates. However, fewer participants were familiar with specific details: its metabolism (n=117; 45.5%), administration routes (n=108; 42%), protein binding (n=90; 35.5%), mechanism of action (n=81; 31.5%), and indications (n=51; 19.8%) [Table3]. Despite these gaps in knowledge, 241 (93.8%) residents recommended Levetiracetam in their practice and 142 (55.3%) of participants preferred levetiracetam as the first line of treatment due to its fewer side effects and effectiveness as mentioned by 43.9% and 40.8%, respectively [Table 4,5].

Table 1 The characteristics of resident doctors (N= 257)

	N	**%**
Gender		
Female	178	69.3
Male	79	30.7
Age (Yrs.)		
20-30	128	49.8
31-40	119	46.3
>40	10	3.9
Years of residency		
R1	52	20.2
R2	29	11.3
R3	68	26.5
R4	108	42.0

Overall, 158 (61%) participants were classified as having poor knowledge of Levetiracetam in neonatal seizures, while 99 (39%) had good knowledge. Male residents exhibited better knowledge levels compared to females (53.2% vs. 32%; P=0.024). Knowledge was significantly higher among residents older than 40 years (50%) compared to their younger counterparts (P=0.037) [Table 6]. Additionally, fourth-year residents had better knowledge levels (58.3%) compared to those in earlier years (R3: 30.8%, R2: 24.1%, R1: 15.4%), with differences being statistically significant (P=0.000) [Table 7]. Participants working in tertiary hospitals also demonstrated higher knowledge levels (41.1%) compared to those in secondary (39.5%) and primary hospitals (20%), with these differences being statistically significant (P=0.042) [Table 8].

Table 2 The practice regarding first-line treatment in neonatal seizure among resident doctors (N= 257)

	N	**%**
First line of treatment used for in-hospital		
Phenytoin	193	75.1
Phenobarbitone	49	19.1
Benzodiazepines	9	3.5
LEV	6	2.3
Used as		
Combination	220	85.6
Monotherapy	37	14.4

Table 3 The practice of levetiracetam among resident doctors (N= 257)

	N	**%**
Treated neonatal seizure with LEV (Yes)	201	78.2
Used as		
Combination	152	59.1
Monotherapy	49	19.1
LEV combined with		
Phenytoin	65	25.3
Phenobarbitone	60	23.4
Phenytoin and phenobarbitone	17	6.6
Na valproate	4	1.6
Midazolam	2	0.8
Phenobarbitone and midazolam	2	0.8
Phenytoin and midazolam	2	0.8

Table 4 The knowledge about levetiracetam use among resident doctors (N= 257)

	N	%	Correct response
Heard about LEV	247	96.1	Yes
Know LEV as anticonvulsant for NS	214	83.3	Yes
LEV can be administered to neonates	213	82.9	Yes
Site of LEV metabolism	117	45.5	Kidneys
Route of administration	108	42	Oral and IV
Know protein binding LEV	90	35	Lower
Know LEV mechanism of action	81	31.5	Binding to SV2A
Know LEV indications	51	19.8	Gen. tonic-clonic, Partial, Myoclonic

Table 5 The perceptions of residents regarding preferring levetiracetam as first-line treatment (N= 257)

	N	%
Prefer LEV as first line of treatment (Yes)	142	55.3
Cause of choosing LEV as first line of treatment		
Less side effect	113	43.9
Effective	105	40.8
No drug-drug interactions	64	24.9
Available	62	24.1

Table 6 The association between knowledge about levetiracetam use and residents' age

	Knowledge		P. value
	Good	Poor	
Age (Yrs.)			
20-30	50	78	0.037
	39.1%	60.9	
31-40	44	75	
	37.0%	63.0%	
>40	5	5	
	50%	50%	

Table 7 The association between knowledge about levetiracetam use and years of residency

	Knowledge		P. value
	Good	Poor	
Years of residency			
R1	8	44	0.000
	15.4%	84.6	
R2	7	22	

	24.1%	75.9%	
R3	21	47	
	30.8%	69.2	
R4	63	45	
	58.3%	41.7	

Table 8 The association between knowledge about levetiracetam use and levels of care

	Knowledge		**P. value**
	Good	**Poor**	
Levels of care			
Primary	4	16	0.042
	20.0%	80.0%	
Secondary	58	89	
	39.5%	60.5%	
Tertiary	37	53	
	41.1%	58.9%	

4. Discussion

The growing interest in Levetiracetam (LEV) for treating neonatal seizures stems from the decreasing effectiveness and adverse neurodevelopmental outcomes associated with traditional therapies. This study assessed the knowledge and practices of 257 pediatric residents regarding the use of Levetiracetam in neonatal seizures.

Almost all participants (99.2%) reported having observed or managed neonatal seizures, with hypoxic-ischemic encephalopathy (HIE) identified as the primary cause in 98.1% of cases. These findings align with those of Nemati H et al. [13] and are supported by reports from Claudia Basti et al., Westergren H et al., and Jayakara Shetty, who highlight HIE as a common cause of symptomatic neonatal seizures, occurring at rates of 1–5 and 8 per 1000 live births [14,15,16]. HIE is a major contributor to neonatal mortality and long-term disability, accounting for 6%–9% of all neonatal deaths and 21%–23% of deaths in term infants. Globally, HIE is estimated to cause over 1 million deaths annually, with outcomes varying significantly based on the severity of encephalopathy [17].

In our study, phenytoin was the first-line treatment for neonatal seizures in most cases (75.1%). This preference likely reflects the prevailing practices and guidelines within the hospitals. Currently, worldwide, phenobarbital and phenytoin are considered first-line treatments, despite concerns about their efficacy and potential side effects, which include neuronal apoptosis and long-term neurological damage [7].

In this study, 55.3% of participants favored Levetiracetam as a first-line treatment, citing its reduced side effects (43.9%) and effectiveness (40.8%) as primary advantages. Phenobarbital, while the most commonly used first-line treatment for neonatal seizures, achieves seizure control in only 40%–50% of cases after a loading dose and up to 70% with repeated doses. For seizures unresponsive to phenobarbital, second-line drugs like phenytoin and midazolam are commonly employed. Levetiracetam has been used as a first-, second-, and third-line treatment in neonates, showing strong efficacy and a favorable safety profile across all age groups. It has a broad antiepileptic spectrum, does not induce apoptosis in the developing rodent brain, and mitigates neurodegeneration in hypoxia-ischemia rodent models. Research shows that Levetiracetam can achieve over 50% seizure reduction within 24 hours and may slightly enhance 24-hour seizure freedom rates. [18,19,20].

However, 61% of participants demonstrated poor knowledge about Levetiracetam's use in neonatal seizures, which is notably lower compared to Fahad A et al.'s study in Saudi Arabia, where knowledge scores were also low regarding

Levetiracetam for neonatal febrile seizures [21]. This lack of knowledge among participants may result from inadequate training, insufficient guidelines, and limited in-service education.

The study revealed that higher levels of knowledge were associated with male residents compared to females (P=0.024) and with older residents (>40 years) (P=0.037). Although the literature on the correlation between knowledge and the age or gender of medical practitioners is limited, these findings suggest that experience may enhance knowledge. Knowledge levels were higher among fourth- and third-year residents compared to those in their earlier years (P=0.000). Additionally, residents in tertiary hospitals exhibited higher levels of knowledge compared to those in secondary and primary hospitals (P=0.042).

5. Conclusion

This study found that phenytoin was predominantly used as the first-line treatment for neonatal seizures among participants. Additionally, most residents used Levetiracetam, often in combination with phenytoin and phenobarbital. Levetiracetam was preferred by many as a first-line treatment due to its reduced side effects and effectiveness. However, overall knowledge about Levetiracetam was inadequate, with participants particularly lacking an understanding of its protein binding, mechanism of action, and indications. Better knowledge levels were associated with being male, older age (>40 years), advanced residency years (R4 and R3), and working in tertiary hospitals.

Recommendations

- In-service and undergraduate medical training on neonatal seizures and the use of Levetiracetam are strongly recommended.
- Further research is needed to explore additional factors influencing the knowledge and management of neonatal seizures among clinical practitioners.

Compliance with ethical standards

Acknowledgments

The researchers independently funded this study.

Disclosure of conflict of interest

The authors declare that they have no conflicts of interest.

Statement of ethical approval

Ethical approval was obtained from the Sudan Medical Specialization Board (SMSB). Consent was secured from hospital authorities. Data were anonymized using identification numbers rather than names to ensure participant confidentiality and were securely stored in separate files

Statement of informed consent

No individual participants were identified in the study reports, and only the study staff had access to participants' identities.

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