Original Article

http://journals.sbmu.ac.ir/jpn
https://doi.org/10.22037/jpn.v9i4.35762

Prevalence of Renal Complications of Levetiracetam in Neonates with Seizures in Qom from 2015 to 2020

Alireza Saadati[1,3],
Mohsen Akhavan Sepahi[2, 3*],
Masoud Hassanvand Amouzadeh[3, 4],
Amir Hamta [5],
Shahab Ahmadi [3]

[1]Department of Neonatology, School of Medicine, Qom University of Medical Sciences, Qom, Iran.
[2]Department of Pediatric Nephrology, School of Medicine, Qom University of Medical Sciences, Qom, Iran.
[3]Pediatric Clinical Research of Development Center, Hazrat Masoomeh Hospital, Qom University Of Medical Sciences, Qom, Iran.
[4]Neuroscience Research Center, Qom University of Medical Sciences, Qom, Iran.
[5]Department of Biostatics, Arak University of Medical Sciences, Arak, Iran.

[*]**Corresponding Author**
Dr. Mohsen Akhavan Sepahi,
Email: akhavansepahim@yahoo.com

Received: August, 2021
Revised: September, 2021
Accepted: December, 2021

Abstract

Background and Aim: Spasms or seizures during the first month of life are the most common clinical manifestations of central nervous system failure in infants and occur due to overactivity of a group of nerve cells in the brain and excessive electrical stimulation of neurons. The purpose of the present study was to evaluate the prevalence of renal complications of levetiracetam in neonates with seizures.

Methods: A retrospective descriptive-analytical study was conducted to evaluate the levels of creatinine and blood urea as well as t duration of levetiracetam use in all neonates. Renal ultrasound was only performed for cases with elevated creatinine levels. Finally, the obtained data were analyzed.

Results: No significant differences were found between neonatal subgroups, especially in infants on levetiracetam, except a transient increase in creatinine and urea levels. During the 6-month follow-up, only three cases had increased creatinine levels above 1.4. These three cases had normal genitourinary ultrasound. In addition, of neonates diagnosed with choroid cyst on ultrasound, the creatinine level was above 1.4 in one case and below 1.4 in other cases.

Conclusion: According to the results of the present study, no serious renal complication was observed with levetiracetam and its use can be recommended for patients.

Keywords: Seizure; Levetiracetam; Renal Complications; Infants.

Conflict of interest: The authors declare no conflict of interest.
Please cite this article as: Saadati A, Akhavan Sepahi M, Hassanvand Amouzadeh M, Hamta A, Ahmadi S. Prevalence of Renal Complications of Levetiracetam in Neonates with Seizures in Qom from 2015 to 2020. J Ped Nephrol 2021;9(4):1-5.
https://doi.org/10.22037/jpn.v9i4.35762

Introduction

Seizure is the most common symptom of nervous system disease in neonates. Seizure is defined as a sudden change in autonomic, activity, behavior, sensory function due to abnormal electrical discharge to the brain (1-3). Convulsions are more common in infancy than in other periods of life. Seizures occur in 1-5 babies per 1,000 live births (4). The most common cause (75% -50%) of seizure in infants is asphyxia or hypoxic-ischemic encephalopathy (2). Other causes include infections, traumas, metabolic disorders, intracranial and intraventricular hemorrhages, and structural abnormalities of the brain (5-8). Neonatal seizures are one of the most common causes of hospital admissions at this age, which may manifest themselves in different patterns (7). Most neonatal seizures improve completely, while some of them lead to transient or chronic complications (7). The human brain grows and develops significantly in the first five years of life, so recurrent seizures affect not only growth and learning capacity, but also lead to structural changes in the brain. Therefore, it is

essential to control seizures with effective drugs (8-12). The first line of treatment for neonatal seizures (after ruling out electrolyte disturbances and hypoglycemia) is phenobarbital followed by phenytoin (13-15).

In 35-45% of seizures, phenytoin and phenobarbital are not effective as the first line of treatment; therefore, it is required to add another drug. New anticonvulsants (such as topiramate, levetiracetam, and lamotrigine) are recommended in resistant neonatal seizures (13-16).

Most seizures require drug treatment and are not controlled with one drug. The fewer the drugs used, the better for the patient due to the long duration of treatment with antiepileptic drugs; therefore, it is better to choose a drug as adjunct therapy that is effective and well tolerated and has few side effects (13-16).

Levetiracetam is derived from pyrrolidine. Levetiracetam is rapidly and almost completely absorbed after oral administration (99%) and its oral bioavailability (syrup and tablet) is 100% (16-17). The maximum concentration is achieved one hour after oral administration in the fasting state. The plasma half-life of the drug is about 7 hours in adults (17). It is effective in refractory seizures as a first-line treatment or adjunctive therapy. In addition, negligible effects on serum proteins, lack of hepatic metabolism, lack of drug reactions and serious side effects, and lack of neurotoxicity are specific features of levetiracetam (17).

Less than 10% of levetiracetam and its major metabolite are bound to plasma proteins. Its distribution volume in the human body is not subjected to extensive metabolism, and the main pathway of its metabolism is through hydrolysis of the acetamide group.

The cytochrome P450 isoenzyme system is not involved in the metabolism of this drug.

Levetiracetam and its major metabolites are inhibitors of cytochrome P450 isoforms, epoxy hydrolase, and UDP glucuronidation enzymes (16-17). Levetiracetam is excreted by the kidneys, and 66% of the consumed amount is excreted in the urine intact. Therefore, due to the properties of levetiracetam and the side effects of first-line drugs (phenobarbital and phenytoin), the use of this drug is recommended in resistant neonatal seizures.

The aim of this study was to evaluate the renal complications of levetiracetam in neonates with seizures in Qom from 2015 to 2016.

Methods

The present study was a retrospective descriptive-analytical study. The Research Committee of Qom University of Medical Sciences (IR.MUQ.REC.1399.255) approved this study. The medical records of neonates presenting to Hazrat Masoumeh Hospital in Qom that met the inclusion criteria were selected by census sampling. The samples consisted of neonates who used only leutiracetam for seizure control during 1394 to 1399.

The indications for starting treatment with levetiracetam in the neonates included any type of neonatal seizure (tonic, clonic, myoclonic, automatisms, and epileptic spasms) as observed by the treating physician and confirmed by electroencephalography (EEG). The patients were examined for growth and development every month after starting levetiracetam, and serum BUN and Cr levels measured every six months. The levels of creatinine and blood urea and the duration of levetiracetam use were recorded for all neonates. Renal ultrasound was only performed for neonates who had elevated levels of creatinine in follow-ups. Finally, the data were analyzed.

The inclusion criteria were age under 28 days, willingness to participate in the study, need for treatment with levetiracetam, lack of renal dysfunction, and clinical confirmation of seizures by a physician. The exclusion criteria were receiving more than one anticonvulsant drug, seizure due to electrolyte imbalance or hypoglycemia, concomitant use of nephrotoxic drugs, parents' hesitation to join the study, incomplete data, and lack of regular follow-up.

Results

Descriptive results related to demographic and independent variables are presented in Table 1. According to the results, most of the subjects were term infants with colonic seizures occurred in the first week of birth. Of 169 infants, brain ultrasound was normal in 94 and IVH was detected in 42. The results of changes in the serum creatinine six months after treatment with levetiracetam are

Table 1. Descriptive results of subjects

	Percent	Number	Group
Gestational age	84%	142	**Term**
	16%	27	**Preterm**
Type of seizure	63.9%	108	**Clonic**
	9.18%	32	**Tonic**
	17. 2%	29	**Myoclonic**
Cause of seizure	39.1%	66	**Sepsis**
	26%	44	**TTN**
	15.4%	26	**Jaundice**
	10.1%	17	**RDS**
	6.5%	11	**IEM**
	3%	5	**IDM**
Brain ultrasound	55.6%	94	**Normal**
	24.9%	42	**IVH**
	17.2%	29	**Chroid cyst**
	1.8%	3	**Agenesis corpous caleosum**
	0.6%	1	**ICH**

presented in Table 2. According to the results, an increase in serum creatinine above 1.4 was only seen in three cases.

Table 2. Serum creatinine changes in the sixth month

Variable	Percent	Number	Group
Creatinine in the sixth month	98.2%	166	**1.4<**
	1.8%	3	**< 1.4**

The results of changes in serum creatinine in the first month of levetiracetam use compared to the sixth month are presented in Table 3.

Table 3. Comparison of serum creatinine between the first and sixth months (Creatinine changes during 6 months after treatment)

	SD	mean	Min	Max	No.
S Cr	0.3033	0.24	0.50	1.40	169

S Cr: Serum Creatinine, SD: Standard deviation, Min: Minimum, Max: Maximum, No: Number

According to the results, the smallest change was -0.5, and the largest change was 1.4.

The results of changes in serum creatinine six months after levetiracetam administration according to the type of seizure are presented in Table 4,5. According to the results, elevated levels of creatinine were observed in two case with tonic seizures. The results of the relationship between creatinine change and type of seizure are presented in Table 4. No significant relationship was found between creatinine change and seizure type (P = 0.20).

Table 4. Creatinine change and type of seizure

Type of seizure	N	mean ±Sd	Min	Max
Colonic	108	0.2194 ± 0.27291	-0/30	0/70
Tonic	32	0.41093 ±0.3219	-0/50	1/40
Myoclonic	29	0.26468 ±0.2828	-0/20	1/00

Min: Minimum, Max: Maximum

Table 5. Serum creatinine changes in the sixth month according to type of seizure

Variable	Percent	Number	Group
Colonic	100%	108	**1.4 <**
	0	0	**1.4 >**
Tonic	93.8%	30	**1.4<**
	6.2%	2	**1.4>**
Myoclonic	96.6%	28	**1.4 <**
	3.4%	1	**1.4 >**

Discussion

Most of the growth and development in the human brain occurs in the first five years of life, so recurrent seizures not only affect growth and learning capacity but also lead to structural changes in the brain. The main purpose of this study was to evaluate the frequency of renal complications due to levetiracetam usage in neonates. In one study, intravenous levetiracetam was started for eight infants who were resistant to first-line seizure treatment, of whom six were completely cured (18). Molla Mohammadi et al conducted a study to investigate the effect of levetiracetam on refractory seizures in neonates in 2018 in Qom. This study was performed as a clinical trial on 245 infants with

seizures. Levetiracetam syrup was started and 95.3% of seizures were controlled while no response was seen in 4.7% of the patients. When the intravenous form of levetiracetam is not available and the infant does not respond to classic first-line medications, oral levetiracetam may be effective as adjunctive therapy (2). Ramantani et al. studied the safety and efficacy of levetiracetam in neonatal seizures in 2010. The drug was discontinued after 2-4 weeks In i9 cases, while 7 infants received the drug for up to 3 months and no severe side effects were observed (19). OwaisKhan evaluated the use of intravenous levetiracetam for the management of acute seizures in 22 infants in 2010. The majority (86%0 of the patients were discharged with oral levetiracetam and no drug side effects were reported at the time of drug administration (20). In 2014, a study was conducted to investigate the possible effects of levetiracetam on acute renal injury. In this study, a 23-year-old woman with seizures without a history of underlying disease was treated with the above drug. She developed acute kidney damage one day after taking the drug and the serum creatinine level increased over time. This case suggests that the use of levetiracetam may lead to acute kidney damage (21). In a study conducted by Kevin Yau et al., the patients were evaluated for renal complications between 30 and 180 days after drug administration. According to the results of this study, no significant differences were found in the rate of acute renal impairment and serum creatinine levels in those who took levetiracetam (22). In 2020, Burak Erdinc et al. reported a case of acute renal injury caused by levetiracetam in a patient with epilepsy. After two days of treatment with levetiracetam, the patient developed symptoms of acute renal impairment and elevated serum creatinine. After drug discontinuation, renal function returned to normal after 30 days. that the authors concluded that regular renal evaluations should be performed for patients treated with this drug (23). Shiue HJ et al. performed a study to compare different diets of levetiracetam in patients with end-stage renal disease (ESRD). Two different regimens were administered once daily (Daily) versus twice daily (BID) and the results were analyzed prospectively. The effects of levetiracetam were dose-dependent; however, due to fluctuations in renal function in each patient, different plasma levels of levetiracetam were observed (24).

According to the results, there was no statistically significant differences in kidney damage and levels of GFR in infants treated with levetiracetam. The authors just found three cases with increased levels of creatinine during levetiracetam usage.

Limitations

We conducted a single center study on a limited number of patients. Thus, there is a need for larger studies with more participants to confirm the results.

Conclusion

This study is the first extensive investigation of the effects of levetiracetam on renal complications in patients with seizures. However, few studies have evaluated the effect of levetiracetam on renal complications on a case-by-case basis. This study can be considered as the first step to evaluate the renal side effects of levetiracetam, which can be confirmed in future studies.

Acknowledgments

Not declared.

Conflict of Interest

The author declares no conflicts of interest.

Financial Support

The author declares no financial support.

References

1. Razieh F, Sedighah AK, Motahhareh G. Afebrile seizure subsequent to initial febrile seizure. Singapore medical journal. 2012;53(5):349-52.
2. Mollamohammadi M, Amirhoseini ZS, Saadati A, Pirzadeh Z, Amouzadeh MH. Oral levetiracetam as add-on therapy in refractory neonatal seizures. Iranian journal of child neurology. 2018;12(4):103.
3. Dimassi S, Labalme A, Ville D, Calender A, Mignot C, Boutry-Kryza N, et al. Whole-exome sequencing improves the diagnosis yield in sporadic infantile spasm syndrome. Clinical genetics. 2016;89(2):198-204.

4. Glass HC. Neonatal seizures: advances in mechanisms and management. Clinics in perinatology. 2014;41(1):177-90.
5. Marcdante K, Kliegman R. Seizures. Nelson Essentials of Pediatrics 8th ed Philadelphia, PA: Elsevier..2019
6. Le Coz J, Chéron G, Nabbout R, Patteau G, Heilbronner C, Hubert P, et al. Diagnostic evaluation and management of seizures and status epilepticus in children with known epilepsy or new-onset seizures: A retrospective and comparative analysis. Archives de Pédiatrie. 2020;27(2):66-71.
7. Scher M. Neonatal seizures. Epilepsy Syndromes E-Book. 2017:49.
8. Samanta D. Recent Advances in the Diagnosis and Treatment of Neonatal Seizures. Neuropediatrics. 2020.
9. Shellhaas RA, editor Continuous long-term electroencephalography: the gold standard for neonatal seizure diagnosis. Seminars in Fetal and Neonatal Medicine; 2015: Elsevier.
10. Alix V, James M, Jackson AH, Visintainer PF, Singh R. Efficacy of fosphenytoin as first-line antiseizure medication for neonatal seizures compared to phenobarbital. Journal of Child Neurology. 2021;36(1):30-7.
11. Polavarapu A, Hasbani D, editors. Neurological complications of nutritional disease. Seminars in pediatric neurology; 2017: Elsevier.
12. Pisani F, Spagnoli C, editors. Acute symptomatic neonatal seizures in preterm neonates: etiologies and treatments. Seminars in Fetal and Neonatal Medicine; 2018: Elsevier.
13. Meyer JM. Pharmacotherapy of psychosis and mania. Goodman and Gilman's the pharmacological basis of therapeutics. 2011:417-56.
14. Nimaga K, Desplats D, Doumbo O, Farnarier G. Treatment with phenobarbital and monitoring of epileptic patients in rural Mali. Bulletin of the World Health Organization. 2002;80:532-7.
15. Lerman-Sagie T, Lerman P. Phenobarbital still has a role in epilepsy treatment. Journal of child neurology. 1999;14(12):820-1.
16. Wagner CB, Kreimer AM, Carrillo NP, Autry E, Schadler A, Cook AM, et al. Levetiracetam Compared to Phenobarbital as a First Line Therapy for Neonatal Seizures: An Unexpected Influence of Benzodiazepines on Seizure Response. The Journal of Pediatric Pharmacology and Therapeutics. 2021;26(2):144-50.
17. Mruk AL, Garlitz KL, Leung NR. Levetiracetam in neonatal seizures: a review. The Journal of Pediatric Pharmacology and Therapeutics. 2015;20(2):76-89.
18. Rakshasbhuvankar A, Rao S, Kohan R, Simmer K, Nagarajan L. Intravenous levetiracetam for treatment of neonatal seizures. Journal of Clinical Neuroscience. 2013;20(8):1165-7.
19. 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.
20. Khan O, Chang E, Cipriani C, Wright C, Crisp E, Kirmani B. Use of intravenous levetiracetam for management of acute seizures in neonates. Pediatric neurology. 2011;44(4):265-9.
21. Spengler DC, Montouris GD, Hohler AD. Levetiracetam as a possible contributor to acute kidney injury. Clinical therapeutics. 2014;36(8):1303-6.
22. Yau K, Burneo JG, Jandoc R, McArthur E, Muanda FT, Parikh CR, et al. Population-based study of risk of AKI with levetiracetam. Clinical Journal of the American Society of Nephrology. 2019;14(1):17-26.
23. Erdinc B, Ghanta S, Andreev A, Elkholy KO, Sahni S. Acute Kidney Injury Caused by Levetiracetam in a Patient With Status Epilepticus. Cureus. 2020;12(6).
24. Shiue HJ, Taylor M, Sands KA. Comparison of levetiracetam dosing regimens in end-stage renal disease patients undergoing intermittent hemodialysis. Annals of Pharmacotherapy. 2017;51(10).5-862:
25. Patsalos PN. Pharmacokinetic profile of levetiracetam: toward ideal characteristics. Pharmacology & Therapeutics. 2000;85(2):77-85.
26. Morrell MJ, Leppik I, French J, Ferrendelli J, Han J, Magnus L. The KEEPER™ 1KEEPER is a trademark of UCB S.A.1 trial: levetiracetam adjunctive treatment of partial-onset seizures in an open-label community-based study. Epilepsy Research. 2003;54(2):153-61.
27. Beran RG, Berkovic SF, Black AB, Danta G, Hiersemenzel R, Schapel GJ, et al. Efficacy and safety of levetiracetam 1000–3000mg/day in patients with refractory partial-onset seizures: a multicenter, open-label single-arm study. Epilepsy Research. 2005;63(1):1-9.
28. Tanaka S, Tanaka T. Levetiracetam add-on therapy in Japanese patients with refractory partial epilepsy. Epileptic disorders. 2013;15(2):132-41.
29. Noyer M, Gillard M, Matagne A, Hénichart J-P, Wülfert E. The novel antiepileptic drug levetiracetam (ucb L059) appears to act via a specific binding site in CNS membranes. European journal of pharmacology. 1995;286(2):137-46.
30. Wu XY, Hong Z, Wu X, Wu LW, Wang XF, Zhou D, et al. Multicenter double-blind, randomized, placebo-controlled trial of levetiracetam as add-on therapy in Chinese patients with refractory partial-onset seizures. Epilepsia. 2.405-398:(3)50;009
31. Cataldi M, Lariccia V, Secondo A, Di Renzo G, Annunziato L. The antiepileptic drug levetiracetam decreases the inositol 1, 4, 5-trisphosphate-dependent [Ca2+] I increase induced by ATP and bradykinin in PC12 cells. Journal of Pharmacology and Experimental Therapeutics. 2005;313(2):720-30.