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The Clinical Efficacy and Safety of Acute Care Setting for Intravenous Levetiracetam (Focale) in Children

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Abstract

Background Status epilepticus (SE) is a serious neurological emergency with a high mortality rate. Although levetiracetam is an effective antiepileptic drug for managing SE, its excessive cost may limit its accessibility. Focale, a more affordable generic version, is currently available and is more than 50% less expensive than the original version. However, there is currently no study on the efficacy and safety of Focale in pediatric patients with SE.

Objective This study aimed to investigate the efficacy and safety of the antiepileptic drug, Focale, in pediatric patients.

Materials and Methods This was a retrospective study that examined 131 pediatric patients younger than 18 years, who were treated with Focale for seizure control and prevention between June 2019 and November 2022.

Results A total of 131 patients were included in the study, of which 73 (55.7%) were male. The age group with the highest frequency was 0 to 3 years old (28.2%). Focale was used with the following indications: (1) SE (45.04%), (2) acute repetitive convulsive seizures (22.14%), (3) primary prophylaxis (26.72%), (4) acute first seizure (1.52%), and (5) patients with epilepsy with nothing per oral (4.58%). Regarding the outcomes, the seizure-controlled rate in the seizure group was 81.1%, while the seizure prevention rate was 92.7% for those who received Focale as a seizure prophylaxis. Only 2 out of 131 patients had experienced adverse effects (1.5%).

Keywords
- Focale
- levetiracetam
- children
- efficacy
- safety

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Conclusion The generic intravenous levetiracetam treatment had high seizure-controlled rate in patients with seizure attacks and seizure prevention rate in the seizure prophylaxis group in pediatric patients. Side effects of this regimen in pediatric patients were low.

Introduction

Status epilepticus (SE) is a neurological emergency characterized by continuous seizures lasting more than 5 minutes.[1] It has an annual incidence of ~20 per 100,000 population.[2] Benzodiazepines are first-line drugs for the treatment of SE. However, it has been found that about one-third of patients do not respond to benzodiazepine treatment.[3] Patients, who cannot quickly control their seizures, may suffer long-term neurological deficits, cognitive dysfunction, and behavioral abnormalities.[4] The second-line antiepileptic drugs (AEDs) for SE include phenytoin, fosphenytoin, sodium valproate, and levetiracetam.[3,5] A meta-analysis that included data from seven randomized controlled trials and six observational studies, which had a total of 1,575 patients with ages between 2.3 and 6.1 years, compared the efficacy of levetiracetam with phenytoin or fosphenytoin.[6] The study discovered no significant difference in seizure cessation rates, ICU admissions, intubations, and drug side-effects between levetiracetam, phenytoin, and fosphenytoin. In addition, these findings were determined to be consistent with the ESETT study performed by Chamberlain et al.[7]

A systematic review and a meta-analysis were conducted to evaluate the efficacy of levetiracetam in 1,188 infants.[8] The study revealed that levetiracetam had comparable efficacy to phenobarbital, with a seizure control rate of 45%. Additionally, levetiracetam was associated with having fewer adverse effects.

Levetiracetam is an AED currently used in hospitals under the brand name, Keppra. However, the high cost of this drug poses a challenge, particularly in developing countries where affordability is a significant concern. To address this issue, Srinagarind Hospital in Thailand has transitioned from Keppra to a locally produced generic drug called, Focale, which is more than 50% cheaper. Nonetheless, the limited research on the efficacy and safety of Focale raises questions about its suitability for use in medical settings.

To evaluate the efficacy and safety of Focale, Wongjirattikarn et al conducted a study comparing Keppra and Focale in the treatment of SE and acute repetitive convulsive seizures (ARCS).[9] The study involved administering levetiracetam intravenously to patients and assessing their response to the two brands of medication. The results of the study showed no significant differences in efficacy or safety between the two brands of medication. This factor indicated that Focale may be a viable alternative to Keppra in the management of these conditions.

At present, Focale is being used at Srinagarind Hospital instead of Keppra, and they have been found to be equally effective and safe. However, no study has been conducted on the efficacy and safety of Focale in pediatric patients (aged 18 years or younger) in Srinagarind Hospital or in other hospitals worldwide. Therefore, to provide information for patient care and the development of AEDs management policies in other hospitals, researchers are interested in studying the efficacy and safety of Focale in pediatric patients with SE, ARCS, and primary prophylaxis in patients undergoing neurosurgery for brain disorders. This study aimed to investigate the effectiveness and safety of the medication, levetiracetam, marketed as Focale, in pediatric patients.

Materials and Methods

A retrospective study was conducted. The processes included collecting data from medical records and electronic databases of pediatric patients (aged below 18 years), who were administered the medication levetiracetam via intravenous injection, marketed as Focale. The data of a total of 131 patients were collected from June 2019 to November 2022. This study was approved by the Human Research Ethics Committee of Khon Kaen University and was given the reference number HE661019.

The data collection tool consisted of collecting information on gender, age, diagnosis of seizure, the dosage of levetiracetam medication, seizure control after medication, and other AEDs that had been received by the patients, as well as the data on the effectiveness and safety of levetiracetam sold under the name of Focale.

The study population was categorized into two groups: seizure group and primary prophylaxis group. The seizure group defined by those who had seizure attack was categorized into three groups: SE, acute seizure, and first seizure. The primary prophylaxis group received Focale to prevent seizure and composed of patients who underwent surgery and those who required nothing per oral (NPO) treatment.

Definition of Seizure Control

For those who had seizure attack, there were three seizure outcomes: “Controlled seizure” refers to the patients, who have had no seizures after receiving the Focale medication within 30 minutes and had no seizure until discharge. “Uncontrolled seizure” refers to those patients, who had continued to experience seizures after receiving the Focale medication within 30 minutes. “Recurrent seizure” refers to the patients, who had stopped having seizures after receiving Focale medication within 30 minutes, but seizure

was recurrent within 24 hours and required additional treatment with Focale.

For those who were treated for seizure prophylaxis, there were two outcomes: "No seizure" refers to those patients who had had no seizures after receiving the Focale medication. And those who had "seizure attack" were epileptic patients, who had not experienced seizures prior to admission but who had developed seizures after surgery or NPO.

Data Analysis

The characteristics of samples were expressed as frequencies and percentages for the categorical data and means with standard deviations (SDs) or medians with minimum and maximum values for continuous data, depending on the distribution of data.

The efficacy and adverse effects of levetiracetam (trade name: Focale) were reported as percentages and 95% confidence intervals (CIs). All statistical analyses were performed using STATA software (StataCorp, College Station, Texas, United States).

Results

A total of 131 pediatric patients under the age of 18 were included in this study, with 73 males and 58 females. The age group of 0 to 3 years had the highest frequency with 37 cases (28.2%), and 121 patients (92.4%) had comorbidities, as shown in ►**Table 1**.

The study results regarding the use of the Focale medication were as follows: 78 patients (59.5%) received Focale as the first-line treatment, 46 patients (35.1%) received it

Table 1 Demographic data and comorbidity of pediatric patients who received intravenous generic levetiracetam Focale ($n = 131$)

Characteristics	*n*	(%)
Sex		
Male	73	(55.7%)
Female	58	(44.3%)
Age (y)		
0–3	37	(28.2%)
3.1–6	21	(16.0%)
6.1–9	12	(9.2%)
9.1–12	16	(12.2%)
12.1–15	20	(15.3%)
15.1–18	22	(16.8%)
> 18	3	(2.3%)
Mean (SD)	8.37	(6.20)
Median (min:max)	8.75	(0.0025: 18.75)[a]
Weight (kg) ($n = 129$)		
Mean (SD)	29.08	(21.19)
Median (min:max)	25.6	(0.84: 92)
Height (cm) ($n = 113$) Mean (SD)	119.00	(39.27)
Length of stay (days)		
Mean (SD)	29.34	(34.45)
Median (min:max)	16	(2: 258)
Comorbidities		
Comorbidity		
No	10	(7.6%)
Yes[b]	121	(92.4%)
- Renal disease	15	(11.45)
- Liver disease	9	(6.9%)
- Heart disease	12	(9.2%)
- CNS anomaly	84	(64.1%)
- Congenital anomaly	15	(11.5%)

(*Continued*)

Table 1 (*Continued*)

Characteristics	*n*	(%)
- Thalassemia	9	(6.9%)
- Others (►**Supplementary Table S1**, available in the online version)	101	(77.1%)
Baseline laboratory data (before starting Focale)		
SCR ($n = 119$)		
Mean (SD)	0.59	(0.54)
Median (min:max)	0.50	(0.06: 4.91)
AST (U\L) ($n = 58$)		
Mean (SD)	171.10	(544.39)
Median (min:max)	39	(3: 3471)
ALT (U\L) ($n = 58$)		
Mean (SD)	200	(901.75)
Median (min:max)	33	(1: 6845)
EEG		
Negative	112	(85.5%)
Positive	19	(14.5%)
MRI/CT brain		
No	41	(31.3%)
Yes	90	(68.7%)
Complications		
No	26	(19.9%)
Yes[c]	105	(80.1%)
- Pneumonia	27	(20.6%)
- Urinary tract infection	13	(9.9%)
- Septicemia	22	(16.8%)
- Arrhythmia	1	(0.8%)
- Renal impairment	9	(6.9%)
- Respiratory failure	17	(13.0%)
- Shock	8	(6.1%)
- Pressure sore	0	(0.0%)
- Deep vein thrombosis	5	(3.8%)
- GI bleeding	0	(0.0%)
- Hypotension	2	(1.5%)
- Pulmonary embolism	3	(2.3%)
- Confusion	4	(3.1%)
- Visual blurring	3	(2.3%)
- Others (►**Supplementary Table S2**, available in the online version)	101	(77.1%)

[a]Minimum age is 1 day and the maximum age is 18.75 years.
[b]Patient had more than one comorbidity.
[c]Complication can answer as multiple diseases.

as second-line treatment, 6 patients (4.6%) received it as a third-line treatment, and 1 patient (0.8%) received it as fourth-line treatment (►**Table 2**). There were 24 patients (18.3%) who experienced seizure recurrence within 24 hours after receiving Focale medication. These patients were in the SE group (23 patients) and ARCS group (1 patient) as shown in ►**Table 2**. There were 20 patients who required reloading of Focale: 19 patients in the SE group (82.6%) and 1 patient in the ARCS group (100%). All 20 patients had seizure controlled after reloading of Focale. ►**Table 3** presents the number and rank of AEDs used in patients, as well as the rank of the Focale medication in the treatment regimen.

Table 2 Study drug administration of pediatric patients who received intravenous generic levetiracetam Focale ($n = 131$)

Variables	Status epilepticus ($n = 59$)		Acute seizure ($n = 29$)		First seizure ($n = 2$)		Primary prophylaxis ($n = 35$)		NPO ($n = 6$)		Total ($n = 131$)	
	n	(%)	*n*	(%)	*n*	(%)	*n*	(%)	*n*	(%)	*n*	(%)
Amounts of AED												
1	21	(35.6%)	11	(37.9%)	1	(50.0%)	28	(80.0%)	6	(100.0%)	67	(51.2%)
2	27	(45.8%)	16	(55.2%)	1	(50.0%)	7	(20.0%)	0	(0.0%)	51	(38.9%)
3	8	(13.5%)	2	(6.9%)	0	(0.0%)	0	(0.0%)	0	(0.0%)	10	(7.6%)
4	2	(3.4%)	0	(0.0%)	0	(0.0%)	0	(0.0%)	0	(0.0%)	2	(1.5%)
5	1	(1.7%)	0	(0.0%)	0	(0.0%)	0	(0.0%)	0	(0.0%)	1	(0.8%)
Mean (SD)	**1.90**	**(0.88)**	**1.69**	**(0.60)**	**1.50**	**(0.71)**	**1.20**	**(0.41)**	**1**	**(0.0)**	**1.62**	**(0.76)**
Order of Focale												
1	28	(47.4%)	13	(44.8%)	1	(50.0%)	30	(85.7%)	6	(100.0%)	78	(59.5%)
2	26	(44.1%)	14	(48.3%)	1	(50.0%)	5	(14.3%)	0	(0.0%)	46	(35.1%)
3	4	(6.8%)	2	(6.9%)	0	(0.0%)	0	(0.0%)	0	(0.0%)	6	(4.6%)
5	1	(1.7%)	0	(0.0%)	0	(0.0%)	0	(0.0%)	0	(0.0%)	1	(0.8%)
Previous IV AED												
No	29	(49.1%)	14	(48.3%)	1	(50.0%)	29	(82.9%)	6	(100.0%)	79	(60.3%)
Yes	30	(50.9%)	15	(51.7%)	1	(50.0%)	6	(17.1%)	0	(0.0%)	52	(39.7%)
AED after Focale												
No	48	(81.4%)	27	(93.1%)	2	(100.0%)	35	(100.0%)	6	(100.0%)	118	(90.1%)
Yes	11	(18.6%)	2	(6.9%)	0	(0.0%)	0	(0.0%)	0	(0.0%)	13	(9.9%)
LD of Focale												
No	9	(15.3%)	5	(17.2%)	0	(0.0%)	19	(54.3%)	4	(66.7%)	37	(28.2%)
Yes	50	(84.7%)	24	(82.8%)	2	(100.0%)	16	(45.7%)	2	(33.3%)	94	(71.8%)
Dose of loading dose ($n = 94$)												
Mean (SD)	660.82	(546.06)	1035.83	(551.39)	687	(866.91)	726.88	(405.57)	750	(353.55)	770.27	(541.64)
Median (min:max)	495	(36: 2000)	1000	(280: 2000)	687	(74: 1300)	715	(140: 1600)	750	(500: 1000)	680	(36: 2000)
Seizure control ($n = 94$)												
No	23	(46.0%)	1	(4.2%)	0	(0.0%)	0	(0.0%)	0	(0.0%)	24	(25.5%)
Yes	27	(54.0%)	23	(95.8%)	2	(100.0%)	6	(100.0%)	2	(100.0%)	60	(63.8%)
NA	0	(0.0%)	0	(0.0%)	0	(0.0%)	10	(62.5%)	0	(0.0%)	10	(10.6%)

(*Continued*)

Table 2 (*Continued*)

Variables	Status epilepticus ($n=59$)		Acute seizure ($n=29$)		First seizure ($n=2$)		Primary prophylaxis ($n=35$)		NPO ($n=6$)		Total ($n=131$)	
	n	(%)	*n*	(%)	*n*	(%)	*n*	(%)	*n*	(%)	*n*	(%)
Reloading dose (uncontrolled seizure group, $n=24$)												
No	4	(17.4%)	0	(0.0%)	–	–	–	–	–	–	4	(16.7%)
Yes	19	(82.6%)	1	(100.0%)	–	–	–	–	–	–	20	(83.3%)
Dose of reloading dose (uncontrolled seizure group, $n=20$)												
Mean (SD)	299.32	(373.82)	250	NA	–	–	–	–	–	–	296.85	(364.01)
Median (min:max)	180	(18: 1,500)	NA	NA	–	–	–	–	–	–	190	(18: 1500)
Reloading dose (controlled seizure group, $n=60$)												
No	26	(96.3%)	22	(95.7%)	2	(100.0%)	6	(100.0%)	2	(100.0%)	58	(96.7%)
Yes	1	(3.7%)	1	(4.3%)	0	(0.0%)	0	(0.0%)	0	(0.0%)	2	(3.3%)
Dose of reloading dose (controlled seizure group, $n=2$)												
Mean (SD)	520	NA	1000	NA	–	–	–	–	–	–	760	(339.4)
Median (min:max)	NA	NA	NA	NA	–	–	–	–	–	–	760	(520: 1000)
Seizure control after reloading dose (both uncontrolled and controlled seizure group, $n=22$)												
No	9	(45.0%)	1	(20.0%)	–	–	–	–	–	–	10	(45.5%)
Yes	11	(55.0%)	1	(50.0%)	–	–	–	–	–	–	12	(54.5%)
Second reloading dose (uncontrolled seizure after first reloading dose, $n=10$)												
No	2	(22.3)	0	(0.0)	–	–	–	–	–	–	2	(20.0%)
Yes	7	(77.8%)	1	(100.0%)	–	–	–	–	–	–	8	(80.0%)
Dose of second reloading dose ($n=8$)												
Mean (SD)	288.57	(274.43)	1000	NA	–	–	–	–	–	–	377.50	(357.52)
Median (min:max)	200	(60: 800)	NA	NA	–	–	–	–	–	–	220	(60: 1000)
Seizure control after second reloading dose ($n=8$)												
No	3	(42.9%)	0	(0.0%)	–	–	–	–	–	–	3	(37.5%)
Yes	4	(57.1%)	1	(100.0%)	–	–	–	–	–	–	5	(62.5%)
Loading with other AED												
No	46	(78.0%)	24	(82.8%)	1	(50.0%)	33	(94.3%)	6	(100.0%)	110	(84.0%)
Yes	13	(22.0%)	5	(17.2%)	1	(50.0%)	2	(5.7%)	0	(0.0%)	21	(16.0%)

Abbreviations: AED, antiepileptic drug; NA, not available.

Table 3 Study drug maintenance and laboratory data of pediatric patients who received intravenous generic levetiracetam Focale ($n = 131$)

Variables	Status epilepticus ($n = 59$)		Acute seizure ($n = 29$)		First seizure ($n = 2$)		Primary prophylaxis ($n = 35$)		NPO ($n = 6$)		Total ($n = 131$)	
	n	(%)	*n*	(%)	*n*	(%)	*n*	(%)	*n*	(%)	*n*	(%)
Study drug maintenance												
Maintenance dose of Focale												
No	46	(78.0%)	24	(82.8%)	1	(50.0%)	33	(94.3%)	6	(100.0%)	110	(84.0%)
Yes	13	(22.0%)	5	(17.2%)	1	(50.0%)	2	(5.7%)	0	(0.0%)	21	(16.0%)
Add AED												
No	40	(67.8%)	26	(89.7%)	2	(100.0%)	33	(94.3%)	5	(83.3%)	106	(80.9%)
Yes	19	(32.2%)	3	(10.3%)	0	(0.0%)	2	(5.7%)	1	(16.7%)	25	(19.1%)
Seizure outcome[a]												
Stop seizure	47	(79.7%)	25	(86.2%)	1	(50.0%)	0	(0.0%)	0	(0.0%)	73	(55.7%)
No stop seizure	2	(3.4%)	0	(0.0%)	0	(0.0%)	0	(0.0%)	0	(0.0%)	2	(1.5%)
Stop and recurrent seizure	10	(16.9%)	3	(10.3%)	1	(50.0%)	0	(0.0%)	0	(0.0%)	14	(10.7%)
No seizure	0	(0.0%)	1	(3.5%)	0	(0.0%)	33	(94.3%)	5	(83.3%)	39	(29.8%)
Seizure	0	(0.0%)	0	(0.0%)	0	(0.0%)	2	(5.7%)	1	(16.7%)	3	(2.3%)
Laboratory data (after start study drug)												
SCR ($n = 97$)												
Mean (SD)	0.594	(0.690)	0.585	(0.422)	0.57	NA	0.562	(0.351)	0.498	(0.269)	0.580	(0.549)
Median (min:max)	0.40	(0.13: 4.47)	0.48	(0.16: 1.78)	NA	NA	0.46	(0.24: 1.82)	0.41	(0.30: 0.88)	0.43	(0.13: 4.47)
AST (U\L) ($n = 42$)												
Mean (SD)	166.04	(541.29)	59.17	(60.19)	–	–	108.80	(81.20)	31	NA	125.48	(410.46)
Median (min:max)	43.5	(14: 2695)	39.5	(13: 209)	–	–	84	(59: 252)	NA	NA	43.5	(13: 2695)
ALT (U\L) ($n = 42$)												
Mean (SD)	79.96	(135.93)	56.67	(77.82)	–	–	89.20	(36.32)	22	NA	73.02	(111.00)
Median (min:max)	29.5	(4: 628)	29.5	(17: 298)	–	–	73.0	(65: 153)	NA	NA	37.5	(4: 628)
EEG ($n = 13$)												
Negative	4	(36.4%)	0	(0.0%)	–	–	1	(100.0%)	–	–	5	(38.5%)
Positive	7	(63.6%)	1	(100.0%)	–	–	0	(0.0%)	–	–	8	(61.5%)

[a]95% confidence intervals were reported in ►**Table 4**.

Table 4 Seizure outcomes of pediatric patients who received intravenous generic levetiracetam Focale ($n = 131$)

Seizure outcome	Frequency		Percentage		95% CI
Total ($n = 131$) Seizure group ($n = 90$)					
- Controlled seizure	73		81.1		71.5–88.6%
- Uncontrolled seizure	2		2.2		2.7–7.8%
- Recurrent seizure Prophylaxis ($n = 41$)	14		15.6		8.8–24.7%
- No seizure	38		92.7		80.1–98.5%
- Seizure	3		7.3		1.5–19.9%
Status epilepticus ($n = 59$)					
- Controlled seizure	47		79.7		69.4–89.9%
- Uncontrolled seizure	2		3.4		0.4–11.7%
- Recurrent seizure	10		16.9		7.4–26.5%
Acute seizure ($n = 29$)					
- Controlled seizure	25		86.2		73.7–98.8%
- Recurrent seizure	3		10.3		2.2–27.4%
- Uncontrolled seizure	1		3.5		0.1–17.8%
First seizure ($n = 2$)					
- Controlled seizure	1		50.0		1.3–98.7%
- Recurrent seizure	1		50.0		1.3–98.7%
Primary prophylaxis ($n = 35$)					
- No seizure	33		94.3		86.6–1.00%
- Seizure	2		5.7		0.7–19.2%
NPO ($n = 6$)					
- No seizure	5		83.3		35.9–99.6%
- Seizure	1		16.7		0.4–64.1%

Abbreviation: NPO, nothing per oral.

Regarding the outcomes, the seizure-controlled rate in the seizure group was 81.1%, while the seizure prevention rate was 92.7% for those who received Focale as a seizure prophylaxis (►**Table 4**). The study results regarding the adverse effects of Focale (►**Tables 5** and **6**) revealed that only 2 out of 131 patients had experienced adverse effects (1.5%). These adverse effects were mild and nonserious, consisting of sinus tachycardia and drowsiness, each occurring in only one patient. The study did not find any severe allergic reactions to Focale that would preclude further treatment.

Discussion

The study investigated the seizure-controlled rate/seizure-prevention rate and side-effects of the Focale in pediatric patients under 18 years old. A total of 131 pediatric patients were included in the study. In this study population, the seizure-controlled rate in those who had seizure attack was high at 81.1%, while the prophylaxis group had seizure prevention rate of 92.7% (►**Table 4**). These data indicated that Focale had high seizure-controlled rate in those with seizure particularly in SE (79.7%) or ARCS (86.2%). Additionally, Focale was able to prevent seizure attack in the prophylaxis group, both surgery group (94.3%) and the NPO group (83.3%). The seizure-controlled rate in this pediatric population was slightly higher than that in the previous study in the adult patients (75%).[9] These data may imply that pediatric patients with seizure may have a better response to Focale treatment.

The effectiveness of Focale in controlling seizures was evaluated in a group of 88 patients with SE and ARCS. Among them, 73 patients (83%) had experienced a complete cessation of seizures, while 13 patients (14.8%) had had a temporary cessation followed by a recurrence, and only 2 patients (2.2%) had not experienced any cessation of seizures. In the subgroup of patients undergoing primary prophylaxis and requiring brain surgery, for 33 out of 35 patients (94.3%), the occurrence of seizures had been able to be prevented, while only 2 patients (5.7%) had experienced seizures after the surgery.

Moreover, the findings indicated that the use of levetiracetam had been highly effective in controlling seizures in various forms, such as SE, ARCS, primary prophylaxis, and first acute seizures. In patients undergoing brain surgery and

Table 5 Adverse drug reaction and final outcome of pediatric patients who received intravenous generic levetiracetam Focale ($n = 131$)

Variables	Status epilepticus ($n = 59$)		Acute seizure ($n = 29$)		First seizure ($n = 2$)		Primary prophylaxis ($n = 35$)		NPO ($n = 6$)		Total ($n = 131$)	
	n	(%)	*n*	(%)	*n*	(%)	*n*	(%)	*n*	(%)	*n*	(%)
Adverse drug[a] reaction												
No	58	(98.3%)	29	(100.0%)	2	(100.0%)	35	(100.0%)	5	(83.3%)	129	(98.5%)
Yes	1	(1.7%)	0	(0.0%)	0	(0.0%)	0	(0.0%)	1	(16.7%)	2	(1.5%)
- Tachycardia	–	–	–	–	–	–	–	–	1	(100.0%)	1	(50.0%)
- Drowsiness	1	(100.0%)	–	–	–	–	–	–	–	–	1	(50.0%)
Final outcome												
Discharge status												
- Complete recovery	0	(0.0%)	0	(0.0%)	0	(0.0%)	0	(0.0%)	1	(16.7%)	1	(0.8%)
- Improve	51	(86.4%)	21	(72.4%)	1	(50.0%)	29	(82.8%)	5	(83.3%)	107	(81.7%)
- Not improve	3	(5.1%)	3	(10.3%)	0	(0.0%)	4	(11.4%)	0	(0.0%)	10	(7.6%)
- Dead, no autopsy	2	(3.4%)	2	(6.9%)	0	(0.0%)	1	(2.9)	0	(0.0%)	5	(3.8%)
- Dead, autopsy	2	(3.4%)	3	(10.3%)	1	(50.0%)	1	(2.9%)	0	(0.0%)	7	(5.3%)
- Normal child D/C separately	1	(1.7%)	0	(0.0%)	0	(0.0%)	0	(0.0%)	0	(0.0%)	1	(0.8%)
Type of discharge												
- With approval	44	(74.6%)	21	(72.4%)	1	(50.0%)	24	(68.6%)	6	(100.0%)	96	(73.3%)
- Against advice	3	(5.1%)	2	(6.9%)	0	(0.0%)	2	(5.7%)	0	(0.0%)	7	(5.3%)
- By escape	0	(0.0%)	0	(0.0%)	0	(0.0%)	1	(2.9%)	0	(0.0%)	1	(0.8%)
- By transfer	8	(13.5%)	0	(0.0%)	0	(0.0%)	6	(17.1%)	0	(0.0%)	14	(10.7%)
- Other	0	(0.0%)	1	(3.5%)	0	(0.0%)	0	(0.0%)	0	(0.0%)	1	(0.7%)
- Death	4	(6.8%)	5	(17.2%)	1	(50.0%)	2	(5.7%)	0	(0.0%)	12	(9.2%)
Length of stay												
Mean (SD)	30.9	(29.1)	29.7	(47.7)	6.5	(3.5)	30.6	(33.5)	12.3	(5.4)	29.3	(34.4)
Median (min:max)	18	(4: 115)	15	(2: 258)	6.5	(4: 9)	16	(2: 138)	12.5	(6: 20)	16	(2: 258)

[a]95% confidence intervals were reported in ►**Table 6**.

Table 6 Adverse drug reactions of pediatric patients who received intravenous generic levetiracetam Focale ($n = 131$)

Groups	Adverse drug reaction		
	Frequency	Percentage	95% CI
Total ($n = 131$)	2	1.5	0.2–5.4%
Status epilepticus ($n = 59$)	1	1.7	0.04–9.08%
Acute seizure ($n = 29$)	0	0.0	NA
First seizure ($n = 2$)	0	0.0	NA
Primary prophylaxis ($n = 35$)	0	0.0	NA
NPO ($n = 6$)	1	16.7	0.4–64.1%

Abbreviations: NA, not available; NPO, nothing per oral.

in infants with SE, a high-dose loading of 40 mg/kg and a maintenance dose of 80 to 100 mg/kg/day have been shown to effectively control seizures while maintaining safety.[10] Additionally, studies have found that levetiracetam is effective in treating ARCS and refractory SE in children.[11,12] Furthermore, research has also been conducted on the efficacy of levetiracetam in preventing seizures in patients with traumatic brain injuries.[13,14]

The use of levetiracetam as a first-line treatment for SE and ARCS was observed in 41 out of 88 patients (46.6%). This finding is consistent with a study by Kreimer et al, in which levetiracetam was utilized as a first-line treatment for SE.[15] Furthermore, levetiracetam has shown efficacy in treating SE in infants with hypoxic-ischemic encephalopathy,[16] in preterm infants,[17] and in neurocritical care,[18] as reported in other studies.

This study represents the first investigation of the seizure-controlled rate/seizure prevention rate and safety of the intravenous levetiracetam formulation, Focale, in pediatric patients ranging from newborns to 18-year-old patients. The study, which was conducted in a university hospital, can be compared with a real-world setting. Moreover, Focale demonstrated high efficacy and safety, as well as cost-effectiveness. However, there are some limitations in this study. First, this was a retrospective study which may have some missing data. Second, no predictor of seizure controlled was evaluated.[19–24] Third, there was no active comparator in this study. Therefore, it cannot compare the results with the original medication. Finally, some associated diseases such as sleep apnea were not studied.[25–30] Nonetheless, the results can provide useful information for clinical practice and cost-saving strategies.

Conclusion

The intravenous formulation of the levetiracetam, marketed under the name Focale, was shown to have high seizure-controlled rate in patients with seizure attacks and seizure prevention rate in the seizure prophylaxis group in pediatric patients ranging from newborns to 18 years of age. Focale also had low rate of side effects in pediatric patients.

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Conflict of Interest
None declared.

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Supplementary Material

Supplementary Table S1 Details of other comorbidities ($n = 101$)

Other comorbidities	*n*
Abdominal pain, cerebellar aplasia	1
Absent seizure	1
Acute anemia due to intraoperative blood loss, obesity	1
Acute febrile illness	2
Acute febrile illness, anemia due to chronic disease, SIRS of infection origin	1
Acute respiration failure	1
Anemia	6
Anemia due to Fe deficiency	1
Anemia, coma	1
Anemia, intractable seizure	1
Anemia, iron deficiency, urinary tract infection (UTI)	1
Anemia, seizure	1
Aspiration pneumonia	1
Aspiration pneumonia, gastroesophageal reflux disease (GERD)	1
Aspiration pneumonia, varicella zoster	1
Asthma, anemia	1
Attention to tracheostomy, acute respiratory failure, septic shock, Candida septicemia hospital-acquired pneumonia	1
Autoimmune hemolytic anemia	1
Bacterial meningitis	1
Bronchopulmonary dysplasia, GERD, anemia	1
Carbonic protein energy malnutrition	1
Cardiac rhabdomyolysis, asthma	1
Chemotherapy session for neoplasm, herpes simplex virus mucositis	1
Chemotherapy session for neoplasm, palliative care	1
Chemotherapy session, acute pancreatitis	1
Constipation, spastic hip dislocation with flexion contraction	1
Corneal abrasion	1
Delayed milestone	1
DM, hypothyroidism, adrenal insufficiency	1
Early neonatal sepsis, neonatal seizure	1
Epilepsy, pneumonia, hypokalemia	1
Factor 12 deficiency, gastroesophageal reflux disease	1
Factor XII deficiency, vitamin D deficiency	1
Febrile neutropenia, UTIs	1
Focal seizure, hypovolumic shock, pneumothorax	1
GERD, tracheobronchomalacia	1
Gingivitis and periodontal disease	1
Global delay development, epilepsy	1
Hemorrhage cystitis	1
Hyperglycemia	1
Hypertension	1

Supplementary Table S1 (*Continued*)

Other comorbidities	*n*
Hypoalbuminemia	1
Hypoglycemia, acute respiratory failure	1
Hypnosis of cervical spine, bacterial pneumonia, septic shock, secondary COVID-19	1
Hypothyroid, central diabetes insipidus, blindness	1
Hypothyroidism	1
Hypothyroidism, severe bronchopulmonary dysplasia	1
Infect wound at right lateral malleolus, vitamin D insufficiency, central hypothyroidism	1
Iron deficiency anemia	1
Iron overload	1
Iron overload, acute hemolysis, refeeding syndrome	1
Iron overload, vitamin D insufficiency, IGA deficiency	1
Ischemic encephalopathy	1
Left pneumothorax	1
Left sigmoid herniation, diffuse axonal injury, hypoxic induced encephalopathy, descending transtentorial herniation, subarachnoid hemorrhage, pulmonary hemorrhage	1
Microcephalus	1
Minimal left pneumothorax	1
Multiple dental caries, palliative care	1
Neurogenic bladder, hearing loss	1
Obesity	1
Optic atrophy	1
Persistent depressive disorder, posttraumatic stress disorder, obesity, borderline IQ, suicidal attempt	1
Pneumonia	2
Pneumonia from respiratory syncytial virus, multiple dental caries, vitamin D deficiency, agranulocytosis	1
Pneumonia, acute gastroenteritis, retinopathy of prematurity, bilateral sensorineural hearing loss	1
Posttraumatic, subgaleal hematoma at left parietal, marijuana use, allergic rhinitis	1
Precocious puberty	1
Primary polydipsia, growth hormone deficiency	1
Protein energy malnutrition	1
Psychosis disease with hallucination	1
Pterygium syndrome	1
Pulmonary atresia	1
Pulmonary hypertension	2
Respiration failure, Lennox Gastaut syndrome, GERD	1
Respiratory distress, preterm infant, anemia due to blood loss	1
Secondary hypertension	1
Septic shock, SJS from meropenem	1
Severe septic shock	1
Syndrome of inappropriate secretion of antidiuretic hormone	1
SLE, hypertension, central nervous system vasculitis	1
SLE, hypertension, seizure	1
Status epilepticus, autoimmune hemolytic anemia	1
Sturge weber syndrome with secondary glaucoma, meningitis	1
Subarachnoid hemorrhage	1

(*Continued*)

Supplementary Table S1 (*Continued*)

Other comorbidities	*n*
Subarachnoid hemorrhage, transposition of the grant arteries	1
Subgaleal abscess	1
Suspected invasive aspergillosis with suspected pneumonia with sepsis	1
Symptom of inappropriate antidiuretic hormone, hyponatremia, epilepsy	1
Systemic lupus erythematosus, hypertension	1
Vitamin D deficiency	1
Vitamin D deficiency, malnutrition, G-6-PD deficiency, epilepsy	1
Vitamin D deficiency, UTIs, disseminated intravascular coagulation	1
Vomiting, methyl malonyl acidemia, essential amino acid deficiency, status epilepticus	1

Supplementary Table S2 Details of other complication ($n = 101$)

Other complications	n
Acute bronchitis, pulmonary insufficiency	1
Acute cellulitis	1
Acute pancreatitis	1
Acute posthemorrhagic anemia	1
Acute renal failure, hypoglycemia	1
Adrenal insufficiency, vitamin D deficiency	1
AFI, posttraumatic seizure, hyponatremia	1
Anaphylaxis due to blood transfusion, epilepsy, hypokalemia	1
Anemia	2
Anemia due to acute blood loss, candidiasis, acute intraparenchymal hemorrhage	1
Anemia due to in-born error of metabolism, hyperkalemia, vitamin B12 deficiency	1
Anemia, coma, coagulopathy, thrombocytopenia	1
Anemia, hyperkalemia, constipation, diabetes insipidus	1
Anemia, respiration distress, cardiac murmur	1
Bacterial meningitis, intraoperative massive blood loss, coagulopathy, hyponatremia	1
Bacterial meningitis	1
Bacterial trachelitis	1
Bacterial ventriculitis, SIRS of infection origin, anemia	1
Brain death, metabolic acidosis	1
Brain death, syndrome of inappropriate secretion of antidiuretic hormone (SIADH), hyponatremia, nonconvulsive seizure	1
CNS infection, cry, and frantic	1
Coagulopathy due to trauma, hypothermia due to trauma, severe metabolic acidosis due to trauma, hypomagnesemia, hypocalcemia related to transfusion, cardiopulmonary resuscitation	1
Constipation, meningitis, epilepsy	1
Constipation, neutropenia, cerebral edema	1
Craniotomy with bone removal	1
Dysphagia	1
Exotopia	1
Fatigue	1

Supplementary Table S2 (*Continued*)

Other complications	n
Fatigue, nausea, vomiting	1
Febrile neutropenia	2
Febrile neutropenia, candidiasis	1
Febrile neutropenia, thrombocytopenia, anemia due to chemotherapy, seizure	1
Gastroesophageal reflux disease	1
Grand mal seizure, hyponatremia	1
Grand mal seizure, hyponatremia, disseminated intravascular coagulation osteopenia of prematurity	1
Headache with visual loss	1
Hepatitis from MIS-C	1
Hepatitis, hypokalemia	1
Hypokalemia, hyperkalemia, hypoglycemia	1
Hyperammonemia, hypokalemia, refractory status epilepticus, prolong intubation, pleural effusion	1
Hyperkalemia, focal clonic seizure	1
Hypertension	1
Hypertensive emergency, hyponatremia, hypokalemia	1
Hypertensive encephalopathy	1
Hypokalemia	1
Hypokalemia, anemia due to blood loss	1
Hypokalemia, hypophosphatemia	1
Hypokalemia, pulmonary insufficiency	1
Hypokalemia	1
Hyponatremia, generalized tonic clonic seizure, early cerebritis	1
Hyponatremia, gastroesophageal reflux disease, iron deficiency	1
Hyponatremia, hypocalcemia, hypomagnesemia	1
Hyponatremia, hypokalemia, hypophosphatemia, respiratory syncytial virus nasopharyngitis	1
Hyponatremia, syncope, hypokalemia	1
Hypoxic ischemia encephalopathy, hypernatremia, hypokalemia	1
Incomplete cord compression, SIADH, ketamine-induced seizure, symptomatic hyponatremia, hypokalemia, hypophosphatemia	1
Jaundice	1
Left ankle edema	1
Leg edema, hypertension, bone marrow suppression	1
Liver failure, disseminated intravascular coagulopathy	1
Low birth weight	1
Lupus encephalitis, choreoathetosis, long-term use of systemic steroid	1
Metabolic acidosis, hyponatremia	1
Moderate pulmonary hypertension, fetal anemia suspect red cell membrane defect, acute kidney injury, hepatic failure	1
Nausea, vomiting	1
Osteogenesis imperfecta	1
Palliative care	1
Pitting edema	1
Pneumothorax, seizure, constipation, hypernatremia	1
Posterior epistaxis (left), sinusitis (fungal)	1

(*Continued*)

Supplementary Table S2 (*Continued*)

Other complications	n
Pulmonary hemorrhage	1
Pulmonary hypertension, hypoxia	1
Pulmonary insufficiency due to noncardiac surgery. Anemia due to cardiac blood loss	1
Pulmonary insufficiency nonthoracic	1
Pulmonary insufficiency, constipation, hypokalemia, hyperperfusion	1
Retinal astrocytoma	1
Salmon patch at pos neck	1
Seizure, venous sinus thrombosis, hypokalemia, hypernatremia	1
SIADH, bacterial tracheitis, cerebral salt wasting	1
SIADH, cerebral salt waiting	1
SIADH, constipation, hypertension, hypocalcemia, vitamin D deficiency	1
SIADH, hyponatremia, constipation	1
SJS from meropenem (conjunctivitis)	1
Status epilepticus, pulmonary hemorrhage, SIADH, hyponatremia	1
Status epilepticus, secretory diarrhea	1
Stomach perforation	1
Streptococcus infection	1
Symptomatic seizure, preseptal cellulitis	1
Tachycardia	3
Tachycardia (140–160 bpm)	1
Tachycardia, hypertension	1
Transient DI, anemia due to acute blood loss	1
Upper gastrointestinal bleeding, anemia	1
Urinary infection, cutaneous abscess of trunk, acute diarrhea	1
Urinary retention	1
Urinary tract infection, seizure, due to hyponatremia, hypophosphatemia, hypocalcemia	1
Vertigo, hyponatremia	1
Viral gastroenteritis	1

