The Efficacy and Safety Profile of Generic Intravenous Levetiracetam in a Real-World Setting

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Background: There are 3 main epileptic conditions in hospital settings that may require intravenous antiepileptic treatment: status epilepticus, acute repetitive convulsive seizures, and postoperative seizures. Generic intravenous levetiracetam (IV LEV) (Focal; Great Eastern Drug Co, Bangkok, Thailand), has been reported to have comparable efficacy to original IV LEV for treating status epilepticus and acute repetitive convulsive seizures in a randomized controlled trial. At present, there are limited data on the efficacy and tolerability of generic intravenous LEV in real-world situations.

Objective: This study aimed to evaluate the clinical outcomes of generic IV LEV in a real-world setting.

Methods: A retrospective study and analyses were conducted. All adult patients who used IV LEV at University Hospital, Khon Kaen University, Thailand from June 1, 2019, until February 15, 2020, were included. Data were analyzed and reported in terms of the efficacy and tolerability of generic IV LEV.

Results: Ninety-three patients received IV LEV by 3 indications: status epilepticus, acute repetitive convulsive seizures, and postoperative seizures. The proportions of these 3 indications were 41.94% (39 patients), 9.67% (9 patients), and 48.39% (45 patients), respectively. The average seizure control rate at 24 hours was 89.25%. The seizure control rate was significantly higher in the acute repetitive convulsive seizures and postoperative seizure groups than in the status epilepticus group when generic IV LEV was given as the first-line treatment (75.00% vs 50.00%; P = 0.035). The average length of hospital stay was 18.24 (25.40) days. There was no significant discharge status among the 3 groups (P = 0.348). Moreover, the average mortality rate was 5.38%. Side effects were reported in 14 patients (15.05%). The 2 most common side effects were vomiting and bronchospasm (3 patients; 3.22%). There were 10 patients with uncontrolled seizures at 24 hours (10.75%). The only factor associated with uncontrolled seizures at 24 hours was a history of epilepsy. The uncontrolled seizure group had a higher proportion of epilepsy patients than the seizure-controlled group (70.00% vs 33.73%; P = 0.037). Poor discharge status (not improved/death) was 18.28% (17 patients). There was no significant factor between those with an improved or poor discharge status.

Conclusions: Generic IV LEV was effective and relatively well tolerated in the 3 clinical settings (ie, status epilepticus, acute repetitive convulsive seizures, and postoperative seizures). Further clinical data are still required to confirm the results of this study.

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Introduction

There are 3 main epileptic conditions in hospital settings that may require intravenous antiepileptic drug (AED) treatment: status
epilepticus (SE), acute repetitive convulsive seizures (ARCS), and postoperative seizures.\textsuperscript{1} Levetiracetam (LEV) is a new AED that has low protein binding (<10%).\textsuperscript{2} Other advantages of LEV include few drug–drug interactions, no effect on cytochrome P450, a low rate of drug allergy and side effects, and tolerability in patients with liver impairments.\textsuperscript{3} Finally, LEV is reported to be more effective at seizure control in patients with SE compared with phenytoin.\textsuperscript{4} LEV had a slightly higher seizure control rate than phenytoin (18 out of 22 patients or 82% vs 22 out of 30 patients or 73.3%; P 0.33).

The main issue regarding LEV is its cost, which may be a major limitation in developing countries, despite their access to generic LEV. Previous studies have found that switching from brand to generic oral LEV is well tolerated and provides patients with a good quality of life compared with the name-brand LEV.\textsuperscript{5–7} Among 58 patients who have switched from original therapy to generic LEV, there were no significant differences in seizure attacks. Although several randomized controlled trials showed efficacy of intravenous LEV (IV LEV) over other antiepileptic drugs,\textsuperscript{8–10} only 1 randomized controlled trial evaluated generic IV LEV versus brand-name IV LEV.\textsuperscript{11} Both generic and brand-name IV LEV had comparable effects.\textsuperscript{11} The seizure control rate was slightly higher in the original LEV than in the generic form (75% vs 65%; P 0.490). There are currently limited data on the efficacy and tolerability of generic IV LEV in real-world settings. This study, therefore, aimed to evaluate the clinical outcomes of generic IV LEV in a real-world setting.

**Methods**

This study was a single institution, retrospective chart review. We enrolled adult patients who received generic IV LEV (Focale; Great Eastern Drug Co, Bangkok, Thailand) at University Hospital, Khon Kaen University, Thailand. Pregnant women were excluded from the study. The study period ran from June 1, 2019, to February 15, 2020. Eligible patients were enrolled from the hospital database, and their medical records were reviewed. Data retrieved from medical records were collected by way of a double-check technique to confirm the accuracy of this data (P.R.). The study protocol and case record form were approved by the institutional review board. Informed consent was waived by the decision of the institutional review board.

The baseline characteristics, treatment details of IV LEV (Focale), and outcomes were evaluated. The outcomes were seizure control rate at 24 hours, length of stay, discharge status, and side effects of Focale. The seizure control rate at 24 hours was defined if seizures disappeared clinically within 24 hours without evidence of recurrent seizures. Discharge status was categorized into three types: complete recovery/improved, not improved, and death. Discharge status was evaluated by attending physicians.

**Statistical Analyses**

Descriptive statistics were used to compute the studied variables. Data were reported as mean (SD) for numerical variables and number (proportion) for categorical variables. The differences in numerical variables between 2 groups were executed by the Wilcoxon rank-sum test, whereas differences in numerical variables among 3 groups were compared by 1-way ANOVA method. For significant variables, the Bonferroni method was used to evaluate differences between pair groups. A Fisher exact test was used to compute differences between/among groups for categorical variables. Factors associated with seizure control at 24 hours and discharge status were executed. Statistical analyses were performed by Statas software (College Station, Texas).

**Results**

Ninety-three patients received generic IV LEV (Focale) by 3 indications: SE, ARCS, and postoperative seizures. The proportions of these three indications were 41.94% (39 patients), 9.67% (9 patients), and 48.39% (45 patients), respectively. There was no significant difference in terms of age, sex, glomerular filtration rate, or order of treatment (Table 1) among these 3 groups. A history of epilepsy was found more in the ARCS and SE groups (56.41% and 55.56%, respectively) than in the postoperative seizure group (17.78%). The mean loading doses of the first 2 groups were also significantly higher than the postoperative group (1134, 1166, and 827 mg, respectively; P <0.001).

Regarding outcomes (Table 2), there was no significant difference in seizure control rate within 24 hours among these 3 groups (P 0.125). The overall average seizure control rate of the 3 groups was 89.25% (83 patients) and was highest in the postoperative seizure group (95.56%). The seizure control rate was significantly higher in the ARCS and postoperative seizure groups than in the SE group when generic IV LEV (Focale) was given as the first-line treatment (75.00%; 88.37% vs 50.00%; P 0.035). A subgroup analysis for those with renal adjustment showed no difference in seizure control rates among the 3 groups (80.00% vs 100% vs 90.91%; P= 0.689). There were 4 and 1 patients in the ARCS and postoperative seizure group who received reloading of generic IV LEV (Focale). Seizures were controlled in these 5 patients (100%). Phenytoin was the most common accompanying antiepileptic drug (16 patients). The average length of stay was 18.24 (25.40) days, with a slightly shorter length of stay in the postoperative seizure status.
Discussion

The seizure control rate at 24 hours for the first-line generic IV LEV (Focale) in this real-world setting was more than 80%, just slightly lower than the previous randomized controlled trial\[11\] (58.33% vs 65.00% for the ARCS and SE groups). For SE, the seizure control rate at 24 hours in this study (generic IV LEV, Focale) was quite lower than the previous study conducted using brand-name LEV (4 out of 9 patients [4.4.4.4] vs 31 out of 38 patients [81.68%]).\[4\] For the postoperative seizure group, the seizure control rate at 24 hours for the first-line generic IV LEV (Focale) was 84.44%, which was higher than the ARCS group (61.53%). These results could imply that generic IV LEV (Focale) may have different effects among seizure types as a first-line treatment.

A history of epilepsy was found in 35 patients (37.63%) in this study. For the SE group, a history of epilepsy was found in 55.56% of patients, which is comparable to a previous study that enrolled refractory SE patients (59.7%).\[12\] Because compliance with AEDs is the main issue of seizure occurrence in preexisting epilepsy\[13,14\], a history of epilepsy was found to be higher in the ARCS and SE groups than in the postoperative seizure group (56.41%; 55.56% vs 17.78%). A history of epilepsy was a significant factor between those with and without seizure control at 24 hours (33.73% vs 70.00%; P = 0.037), as shown in Table 3. Patients with refractory SE received a polytherapy of antiepileptic drugs rather

\[\text{Table 2}\]

clinical outcomes and managements of adult patients who received intravenous Levetiracetam (Focale) categorized by indications (n = 93).

| Factors                        | ACRS        | SE          | Postop       | p value |
|-------------------------------|-------------|-------------|--------------|---------|
|                               | n = 39      | n = 9       | n = 45       |         |
| Control within 24 hours       | 32 (82.05)  | 8 (88.89)   | 43 (95.56)   | 0.125   |
| First line iv focale          | 24 (75.00)  | 4 (50.00)   | 38 (88.37)   | 0.035   |
| Second line iv focale         | 6 (18.75)   | 3 (37.50)   | 5 (11.63)    | 0.160   |
| Third line iv focale          | 2 (6.25)    | 1 (12.50)   | 1            | 0.067   |
| Reloading                     | 4 (10.26)   | 1 (2.22)    | NA           | 0.289   |
| Control after re-loading      | 4 (100)     | 1 (100)     | NA           |         |
| Mean (SD) dose reloading, mg  | 1250 (288)  | -           | 1000         | 0.495   |
| Other AED                     |             |             |              | 0.775   |
| Phenytoin                     | 9 (75.00)   | 3 (60.00)   | 4 (66.67)    |         |
| Keppra                        | 2 (16.67)   | 2 (40.00)   | 2 (33.33)    |         |
| Valproic acid                 | 1 (8.33)    | 0           | 0            |         |
| Mean (SD) length of stay, days| 23.58 (34.68)| 20.11 (16.25)| 13.24 (14.52)| 0.173   |
| Outcomes at discharge         |             |             |              | 0.348   |
| Complete /improve             | 33 (84.62)  | 9 (100.00)  | 34 (75.56)   | 0.231   |
| Not improved                  | 3 (7.69)    | -           | 9 (20.00)    | 0.187   |
| Death                         | 3 (7.69)    | -           | 2 (4.44)     | 0.798   |
| Side effects                  | 7 (17.05)   | 1 (11.11)   | 6 (13.33)    | 0.910   |
| Depression                    | 1 (2.56)    | -           | 1 (2.22)     |         |
| Vomiting                      | 3 (7.69)    | -           | -            |         |
| Diarrhea/cough                | 1 (2.56)    | -           | -            |         |
| Nausea                        | -           | -           | 1 (2.22)     |         |
| Bronchospasm                  | -           | -           | 3 (6.67)     |         |
| Weakness                      | 1 (2.56)    | 1 (11.11)   | -            |         |
| Headache                      | -           | -           | 1 (2.22)     |         |
| Suicidal idea                 | 1 (2.56)    | -           | -            |         |

Note. ARCS: acute repetitive convulsive seizures; SE: status epilepticus; data presented as number (percentage) unless indicated otherwise.

\[\text{Table 3}\]

clinical parameters of adult patients who received intravenous levetiracetam (Focale) categorized by seizure control (n = 93).

| Factors                        | Uncontrolled n = 10 | Controlled n = 83 | p value |
|-------------------------------|---------------------|-------------------|---------|
| Mean (SD) age, years          | 38.3 (11.19)        | 44.31 (11.49)     | 0.090   |
| Male                          | 4 (4.000)           | 38 (45.78)        | 0.999   |
| GFR > 80 ml/min/1.73m²        | 7 (70.00)           | 63 (75.90)        | 0.569   |
| Order of Focale®              |                     |                   |         |
| 1st line                      | 7 (70.00)           | 66 (79.52)        |         |
| 2nd line                      | 3 (30.00)           | 14 (16.87)        |         |
| 3rd line                      | 0                   | 3 (3.61)          |         |
| History of epilepsy           | 7 (70.00)           | 28 (33.73)        | 0.037   |
| Treatment indications         |                     |                   |         |
| ARCS                          | 7 (70.00)           | 32 (38.55)        | 0.125   |
| SE                            | 1 (10.00)           | 8 (9.64)          |         |
| Postoperative seizures        | 2 (20.00)           | 43 (51.81)        |         |
| Mean (SD) loading dose, mg    | 975.00 (79.05)      | 990.96 (73.36)    | 0.938   |

Note. GFR: glomerular filtration rate; ARCS: acute repetitive convulsive seizures; SE: status epilepticus; data presented as number (percentage) unless indicated otherwise.

group (13.24 days; P = 0.173). There was no significant discharge status among the 3 groups (P = 0.348). The average mortality rate was 5.38%, and side effects were reported in 14 patients (15.05%). The 2 most common side effects were vomiting and bronchospasm (3 patients; 3.22%). There were 10 patients with uncontrolled seizures at 24 hours (10.75%). The only factor associated with an uncontrolled seizure at 24 hours was a history of epilepsy (Table 3). The uncontrolled seizure group had a higher proportion of epilepsy patients than the seizure-controlled group (70.00% vs 37.33%; P = 0.037). There was no significant difference between the uncontrolled seizure and seizure-controlled groups in terms of age, sex, glomerular filtration rate, loading dose/order of generic IV LEV (Focale), or treatment indication. Poor discharge status (not improved/death) was 18.28% (17 patients). There was no significant factor between those with improved or poor discharge status (Table 4).
than monotherapy if a history of epilepsy was present (63% vs 37%).

Compared with previous randomized controlled trials, in this real-world setting, generic IV LEV gave comparable outcomes for both the ARCS and SE groups.11 This study showed a shorter length of stay and favorable discharge status of 13 days and 75.56% in the postoperative seizure group treated with generic IV LEV (Table 2). These real-world data showed that 15% of patients had minor side effects from the generic IV LEV. The rate of side effects was lower than previously reported (44%).2 These differences may be due to the different ethnicities of the study population (Thai vs Australian). Regarding depression and suicide, these side effects were uncommon (0.7% for depression) and may be multifactorial with respect to suicide.10,17 There is at least 1 case report on LEV-induced diffuse interstitial lung disease in a child, but there is no strong evidence of an association between LEV and asthma.18

This study possesses some limitations. First, the majority of patients in the study were classified as ARCS or postoperative seizure in a single university hospital. Further studies are thus required for real-world data concerning patients with Se, and a larger sample size or multicenter setup is needed for the study to be more generalizable. Second, there is no comparison within the study to Original IV LEV (Keppra). Third, some factors associated with seizures were not studied, such as obstructive sleep apnea and other comorbid diseases.19-21 Fourth, data collection was performed by the first author who was not blinded, which may have resulted in inclusion bias. Finally, newly reported side effects of LEV such as bronchospasm may need to be monitored.

Conclusions

Generic IV LEV was found to be effective and relatively well tolerated in these three clinical settings, but further clinical data will be required to confirm the results of this study.

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Conflicts of Interest

The authors have indicated that they have no conflicts of interest regarding the content of this article.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.curtheres.2021.100648.

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### Table 4

Clinical parameters of adult patients who received intravenous levetiracetam (Focale®) categorized by discharge status (n = 93).

| Factors                              | Improved n = 76 | Not improved/death n = 17 | p value |
|--------------------------------------|-----------------|---------------------------|---------|
| Mean (SD) age, years                 | 44 (18-59)      | 52 (35-58)                | 0.104   |
| Male                                 | 33 (43.42)      | 9 (52.94)                 | 0.592   |
| History of epilepsy                  | 32 (42.11)      | 3 (17.65)                 | 0.095   |
| GFR > 80 ml/min/1.73m²               | 58 (76.32)      | 12 (70.59)                | 0.700   |
| Order of Focale®                      |                 |                           |         |
| 1st line                             | 62 (81.58)      | 11 (64.71)                | 0.231   |
| 2nd line                             | 12 (15.79)      | 5 (29.41)                 |         |
| 3rd line                             | 2 (2.63)        | 1 (5.88)                  |         |
| Treatment indications                |                 |                           |         |
| ARCS                                 | 33 (43.42)      | 6 (35.29)                 |         |
| SE                                   | 9 (11.84)       | 0                         |         |
| Postoperative seizures               | 34 (44.74)      | 11 (64.71)                |         |
| Median (range) loading dose, mg      | 1000 (500-2000) | 1000 (500-1250)           | 0.402   |

Note. GFR: glomerular filtration rate; ARCS: acute repetitive convulsive seizures; SE: status epilepticus; data presented as number (percentage) unless indicated otherwise.
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