Original Article

Clinical Outcome of Intravenous Levetiracetam in Acute Seizure, Tertiary Care Hospital, Thailand

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Objective: Intravenous levetiracetam has been approved for use as an antiepileptic drug, as well as in cases of acute seizure. There are few reports that detail the clinical data and outcomes in seizure control within 30 minutes and seizure control which is categorized by a treatment prescription of intravenous levetiracetam.

Materials and Methods: This was a retrospective analytical study conducted at Khon Kaen University's Srinagarind Hospital in Thailand. The study period was between January 1, 2010 and December 31, 2014. The inclusion criteria were that patients were over 15 years old and had received intravenous levetiracetam treatment. The main clinical outcomes were seizure control within 30 minutes and seizure control which is categorized by treatment prescription of intravenous levetiracetam. Clinical outcomes were compared between status epilepticus and non-status epilepticus.

Results: During the study period, there were 332 patients who met the study criteria. The average age of the patients was 55.7±20.4 years with nearly equal gender distribution. Of those, 91 patients (27.4%) had status epilepticus and 241 patients (72.6%) had non-status epilepticus. Intravenous levetiracetam was administered as the first line (after initial benzodiazepine), second line, third line and fourth line antiepileptic drug in 192 patients (57.8%), 107 patients (32.2%), 28 patients (8.4%) and 5 patients (1.5%), respectively. The seizure control rate within 30 minutes after administration of intravenous levetiracetam in the status epilepticus was significantly less than in the non-status epilepticus groups (49.5%, 90%; $p<0.001$), but the number of patients who died in status epilepticus and non-status epilepticus groups were not significantly different (31.9%, 33.2%; $p = 0.78$). The seizure control rates of acute seizure patients who received intravenous levetiracetam in first line, second line, third line and fourth line were 86.9%, 81.3%, 57.1% and 20%, respectively.

Conclusion: Intravenous levetiracetam was effective in acute seizures especially in first line treatment.

Keywords: Levetiracetam, Seizure, Status epilepticus

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Epilepsy is a common disease in clinical practice. There were at least 70 million people worldwide who suffered from epilepsy in 2010[1]. Untreated or uncontrolled epilepsy may lead to several serious conditions or complications including status epilepticus. The administration of antiepileptic drugs is the main method used in the treatment of epilepsy, and is aimed at controlling seizures, avoiding side effects, and maintaining a good quality of life[2]. Currently, there are at least 155 antiepileptic products registered in Hong Kong, including new antiepileptic drugs such as levetiracetam and zonisamide[3]. The International League Against Epilepsy (ILAE) reported that further clinical studies are required to evaluate the relevant overall outcomes associated with antiepileptic drugs[4].

Intravenous levetiracetam has been approved for use as an antiepileptic drug, as well as in cases of status epilepticus[5]. Despite the widespread use of intravenous levetiracetam, there are few reports that detail the clinical data and outcomes associated with this antiepileptic drug. This study aimed to evaluate the clinical use of intravenous levetiracetam in patients with acute seizure.

Materials and Methods

This was a retrospective analytical study conducted at Khon Kaen University's Srinagarind Hospital in Thailand. The study period was between January 1, 2010 and December 31, 2014. The inclusion criteria were that patients were over 15 years old, and had received intravenous levetiracetam treatment. The present study protocol was approved by the ethics committee in human research, Khon Kaen University (HE591031).

The medical records of all eligible patients were reviewed. Baseline characteristics, indications for intravenous

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Table 1. Baseline characteristics and treatment of patients with acute seizures who received ivLEV (n = 332)

Factors	Values
Mean age (SD), years	55.7 (20.4)
Female sex	167 (50.3)
Glomerular filtration rate (GFR), ml/min/1.73 m^2	
≥60	127 (38.3)
<60	205 (61.7)
Indications	
Status epilepticus	91 (27.4)
Non-status epilepticus	241 (72.6)
Loading dose, mg/d	
<500	3 (0.9)
500 to 999	75 (22.6)
1,000	167 (50.3)
1,000 to 1,500	73 (22.0)
>1,500	14 (4.2)
Maintenance dose, mg/d	
<500	-
500 to 999	17 (5.1)
1,000	254 (76.5)
1,000 to 1,500	45 (13.6)
>1,500	16 (4.8)
Treatment order	
First-line	192 (57.8)
Second-line	107 (32.2)
Third-line	28 (8.4)
Fourth-line	5 (1.5)

ivLEV = intravenous Levetiracetam

levetiracetam treatment, details regarding intravenous levetiracetam treatment, and clinical outcomes were recorded. The main clinical outcomes were seizure control within 30 minutes and seizure control which is categorized by a treatment prescription of intravenous levetiracetam. Clinical outcomes were compared between status epilepticus and non-status epilepticus. The definitions for clinical terms were as follows: antiepileptic drug treatment prescription in cases of status epilepticus was determined after initial benzodiazepine treatment; seizure control indicated that seizures were under control and there were no recurrent seizures within 24 hours after treatment with intravenous levetiracetam. Statistical analyses, the data of all eligible patients were analyzed using descriptive statistics. Baseline clinical data and treatment with intravenous levetiracetam are presented as mean (SD) or number (percentage). Clinical outcomes were compared between status epilepticus and non-status epilepticus using a Chi-square test, Statistical significance was defined as a *p*-value less than 0.05. All statistical analysis was performed using STATA software version 10.1 (College Station, Texas, USA) and SPSS program version 16 (Chicago, Illinois, USA).

Results

During the study period, there were 332 patients who met the study criteria. The average age of the patients was 55.7±20.4 years with nearly equal gender distribution. Of those, 91 patients (27.4%) had status epilepticus and 241 patients (72.6%) had non-status epilepticus. Intravenous levetiracetam was administered as the first line (after initial benzodiazepine), second line, third line and fourth line

Table 2. Clinical outcomes of patients with acute seizure who received ivLEV (n = 332) categorized by status epilepticus

Outcomes	Status epilepticus (n = 91)	Non-status epilepticus (n = 241)	*p*-value
Seizure controlled within 30 minutes	45 (49.5)	217 (90.0)	<0.001
Seizure controlled within 24 hours	4 (4.4)	4 (1.7)	
Seizure uncontrolled	42 (46.2)	19 (7.9)	
Cannot assess	-	1 (0.4)	
Death	29 (31.9)	80 (33.2)	0.78
Cardiac arrest/shock	2	20	
Gastric perforation	2	2	
Hypovolemic shock	-	2	
Intracerebral hemorrhage	-	1	
Liver failure	-	1	
Pulmonary emboli	-	1	
Respiratory failure	1	4	
Subdural hematoma	-	1	
Septic shock with organ failure	15	26	
Severe hyperkalemia	-	1	
Severe infection/sepsis	4	11	
Severe metabolic dysfunction	3	10	
Multiple organ failure	2	-	

Data presented as number (percentage)
UGBI = upper gastrointestinal bleeding, ivLEV = intravenous Levetiracetam

Table 3. Seizure control of Acute seizure patients who received ivLEV (n = 332) categorized by treatment order of ivLEV (*p*-value <0.001)

Order of ivLEV	Seizure controlled n = 270	Seizure uncontrolled n = 61	Total n = 331
First line	166 (86.9)	25 (13.1)	191
Second line	87 (81.3)	20 (18.7)	107
Third line	16 (57.1)	12 (42.9)	28
Fourth line	1 (20)	4 (80)	5

1 case in First line cannot assess ivLEV
ivLEV = intravenous Levetiracetam

antiepileptic drug in 192 patients (57.8%), 107 patients (32.2%), 28 patients (8.4%) and 5 patients (1.5%), respectively. The seizure control rate within 30 minutes after administration of intravenous levetiracetam in the status epilepticus was significantly less than in the non-status epilepticus groups (49.5%, 90%; $p<0.001$) but the number of patients who died in the status epilepticus and non-status epilepticus groups were not significantly different (31.9%, 33.2%; $p = 0.78$). The seizure control rates of acute seizure patients who received intravenous levetiracetam in first line, second line, third line and fourth line were 86.9%, 81.3%, 57.1% and 20%, respectively.

Discussion

Levetiracetam is a broad-spectrum antiepileptic drug and is approved as adjunctive therapy for focal-onset seizures, myoclonic seizure, juvenile myoclonic epilepsy and primary generalized tonic-clonic seizures in patients six years of age and older[9,10]. The benefit of levetiracetam is its low drug interaction due to independent metabolism via the cytochrome P450 system[11].

In the present study, the most common indication for intravenous levetiracetam treatment was non-status epilepticus (241 patients or 72.6%). Intravenous levetiracetam was prescribed as the first-line treatment at the highest ratio (57.8%) due to low drug interaction[11]. Intravenous levetiracetam was more effective in terms of seizure control in the non-status epilepticus group than in the status epilepticus group (90% vs. 49.5%). In the present study, intravenous levetiracetam had a lower seizure-control rate than it did in a previous study[14]. A study conducted by Oman found that intravenous levetiracetam had a seizure-control rate of 82% in 22 status epilepticus patients. In our previous study, the seizure-control rate of intravenous levetiracetam in cases of status epilepticus was higher than that of sodium valproate (47.06%) and phenytoin (21.62%)[15].

The overall mortality rate for the patients with status epilepticus and non-status epilepticus did not differ significantly. Additionally, the order of intravenous levetiracetam did affect the seizure control (*p*-value <0.001). As previously reported, factors associated with mortality in status epilepticus are varied, but the types of antiepileptic drugs administered is not among them[15-18]. The mortality rates in status epilepticus patients treated with phenytoin and sodium valproate were29.73% and 11.76%, respectively (*p*-value = 0.189)[15]. Early treatment may be associated with status epilepticus mortality[16-18]. Further studies may be needed to confirm the results of the present study in terms of the prescribing of intravenous levetiracetam treatment on seizure control in status epilepticus patients.

There are some limitations to the present study. First, mortality in the present study was not specifically due to seizure and was recorded as in-hospital mortality. No long-term mortality rates were recorded. Second, there was no head to head comparison between antiepileptic drugs.

Conclusion

Intravenous levetiracetam was effective in acute seizures, especially in first line treatment.

What is already known on this topic?

The present study provides indications from the use of the drug, its treatment order and clinical outcome include seizure control of the patients with acute seizure for ivLEV.

What this study adds?

The present study was aimed towards the patient with acute seizure were control within 30 minutes after administration of ivLEV and seizure control which is categorized by a treatment prescription of ivLEV. It was found that ivLEV can use as first line for control seizure within 30 minutes after administration in acute seizure group, not for status epilepticus group.

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Potential conflicts of interest

The authors declare no conflicts of interest.

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ผลลัพธ์ทางคลินิกของยาฉีดเข้าหลอดเลือดดำเลวีไทราซีแทมในชักเฉียบพลัน, โรงพยาบาลตติยภูมิ, ประเทศไทย

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วัตถุประสงค์: ยาฉีดเข้าหลอดเลือดดำเลวีไทราซีแทมได้รับการยอมรับให้ใช้เป็นยากันชัก รวมถึงในผู้ป่วยที่มีภาวะชักแบบเฉียบพลัน (acute seizure) โดยข้อมูลผลลัพธ์ในด้านคลินิกและผลการควบคุมอาการชักภายใน 30 นาที และผลการควบคุมอาการชักในผู้ป่วยที่ได้รับยาเลวีไทยราซีแทมจำแนกตามคำสั่งการได้รับยา ยังมีรายงานจำนวนไม่มาก

วัสดุและวิธีการ: การศึกษานี้เป็นการศึกษาแบบเก็บข้อมูลย้อนหลัง ณ โรงพยาบาลศรีนครินทร์ มหาวิทยาลัยขอนแก่น ประเทศไทย เก็บข้อมูลผู้ป่วยระหว่างวันที่ 1 มกราคม พ.ศ. 2553 ถึงวันที่ 31 ธันวาคม พ.ศ. 2557 ผู้ป่วยที่เข้าเกณฑ์ได้รับคัดเลือกคือผู้ป่วยอายุมากกว่า 15 ปี และได้รับยาฉีดเข้าหลอดเลือดดำเลวีไทราซีแทม ผลลัพธ์หลักทางคลินิกคือการหยุดชักภายใน 30 นาที และการควบคุมอาการชักโดยจำแนกตามคำสั่งการได้รับยา นอกจากนี้ยังมีการวิเคราะห์เปรียบเทียบผลลัพธ์ทางคลินิกระหว่างผู้ป่วยกลุ่มชักต่อเนื่อง (status epilepticus) และไม่ใช่ชักต่อเนื่อง (non-status epilepticus)

ผลการศึกษา: ผู้ป่วยทั้งหมดที่เข้าเกณฑ์การศึกษาคือ 332 ราย อายุเฉลี่ยของผู้ป่วยคือ 55.7±20.4 ปี และมีการกระจายของข้อมูลด้านเพศใกล้เคียงกัน ผู้ป่วยจำนวน 91 ราย (ร้อยละ 27.4) เป็นผู้ป่วยชักต่อเนื่อง และผู้ป่วยจำนวน 241 ราย (ร้อยละ 72.6) เป็นผู้ป่วยที่ไม่ใช่ชักต่อเนื่อง ผู้ป่วยจำนวน 192 ราย (ร้อยละ 57.8) จำนวน 107 ราย (ร้อยละ 32.2) จำนวน 28 ราย (ร้อยละ 8.4) และจำนวน 5 ราย (ร้อยละ 1.5) ได้รับยาฉีดเข้าหลอดเลือดดำเลวีไทราซีแทมเป็นยาอันดับที่หนึ่ง (หลังจากได้รับยากลุ่ม benzodiazepine) อันดับที่สอง อันดับที่สาม และอันดับที่สี่ตามลำดับ การควบคุมอาการชักภายใน 30 นาที ในผู้ป่วยที่มีภาวะชักต่อเนื่องหลังจากได้รับยาฉีดเลวีไทราซีแทม พบว่ามีจำนวนน้อยกว่ากลุ่มที่ไม่ใช่ภาวะชักต่อเนื่องอย่างมีนัยสำคัญทางสถิติ (49.5%, 90%; p<0.001) แต่อัตราการเสียชีวิตของผู้ป่วยทั้งสองกลุ่มไม่แตกต่างกันอย่างมีนัยสำคัญ (31.9%, 33.2%; p = 0.78) อัตราการควบคุมภาวะชักเฉียบพลันจำแนกตามลำดับการได้รับยาฉีดเลวีไทราซีแทมเป็นอันดับที่หนึ่ง อันดับที่สอง อันดับที่สาม และอันดับที่สี่คือ ร้อยละ 86.9, 81.3, 57.1, และ 20 ตามลำดับ

สรุป: ยาฉีดเข้าหลอดเลือดดำเลวีไทราซีแทมมีประสิทธิภาพในการควบคุมชักในผู้ป่วยที่มีภาวะชักเฉียบพลันที่ได้รับยาเป็นลำดับที่หนึ่ง