The efficacy of intravenous sodium valproate and phenytoin as the first-line treatment in status epilepticus: a comparison study

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Abstract

Background: Status epilepticus (SE) is a serious neurological condition and requires prompt treatment. Sodium valproate has been used to treat SE successfully but its role as the first-line antiepileptic drug (AED) is still controversial. This study evaluated the efficacy of intravenous sodium valproate to determine if it is non-inferior to intravenous phenytoin in SE treatment.

Methods: Patients diagnosed as SE during 2003–2010 who were of an age of more than 15 years and received either intravenous sodium valproate or intravenous phenytoin as the first-line treatment were enrolled. Clinical characteristics and outcomes of SE were recorded and analyzed. The differences of outcomes between sodium valproate and phenytoin group were determined by descriptive statistics.

Results: During the study period, there were 37 and 17 SE patients who received intravenous phenytoin and intravenous sodium valproate as the first-line treatment, respectively. All patients received diazepam 10 mg intravenously as a rescue medication before starting the antiepileptic agents if uncontrolled except one patient in the sodium valproate group. There were no significant differences between the phenytoin and sodium valproate groups in all outcome variables including numbers of patients with clinically-controlled seizures, non-dependent patients, time to seizure control, and duration of hospitalization, and death. No serious cardiovascular event such as hypotension occurred in either group.

Conclusion: Intravenous sodium valproate is non-inferior to intravenous phenytoin as the first-line treatment in SE with no significant cardiovascular compromises.

Keywords: Phenytoin, Sodium valproate, Efficacy, Status epilepticus, Comparison

Background

Status epilepticus (SE) is an emergency condition that requires proper and prompt treatment to prevent morbidity and mortality. Intravenous phenytoin is a main medication to treat SE. Recent and new antiepileptic drugs (AED) such as sodium valproate, lacosamide, levetiracetam or topiramate have potential benefits in treatment of SE [1-4].

Previous studies showed that intravenous sodium valproate may be a potential AED to be effective in SE [1,5]. It may be used as the first-line AED in SE with a good seizure control [5]. Unlike phenytoin [6-8], sodium valproate can be used safely and has no potential major cardiovascular compromises such as cardiac arrhythmia or hypotension [9-12]. Sodium valproate therefore may be an appropriate drug as the first-line treatment in SE.

A meta-analysis of five randomized-controlled studies showed that both intravenous phenytoin and sodium valproate were effective in SE treatment [1]. This study aims to investigate the efficacy of both medications in the treatment of SE as the first-line AED. The results will add more information of the efficacy of both drugs on SE in the literature. The study therefore evaluated if intravenous sodium valproate is non-inferior to intravenous phenytoin in SE treatment.

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Methods

SE patients treated at Srinagarind Hospital, Khon Kaen University, Thailand between 2003 and 2010 were enrolled. The inclusion criteria were patients with an age of more than 15 years and received either intravenous phenytoin or intravenous sodium valproate as the first-line treatment.

Status epilepticus (SE) is a condition with persistent seizure more than 5 minutes or the patient does not gain the consciousness during the interictal period [13]. Generalized convulsive SE is defined as recurrent convulsive seizures that may be overt or subtle, symmetric or asymmetric, and are associated with profound coma and bilateral, although often has asymmetric, ictal discharges on electroencephalogram (EEG) [14]. Non-convulsive SE is defined as SE with a change in behavior and/or mental processes from baseline associated or associated with continuous epileptiform discharges in the EEG or in response to treatment [15].

Data were retrieved from medical records including baseline characteristics, previous medical illnesses, causes of SE, laboratory findings, numbers of AED usage, and outcomes of treatment. The outcomes of treatment were numbers of patients with clinically-controlled seizure, time to seizure control, admission duration, patient status after treatment, change of functional status after treatment, and death. Time to seizure control was identified by the total minutes spent from the start of SE treatment to the time until there was no clinical evidence of seizure. Seizure control was defined clinically and/or by EEG. Patient status after treatment was defined by patient’s functional capacity at the discharge date from the hospital and categorized as dependent or non-dependent status. The dependent status was defined as a condition that the patients needed someone to assist them daily life activities and equal to modified Rankin scale (mRs) of two or more. Worsening of functional outcome was defined by change of functional outcome to dependent status or death at discharge date. Mortality rate and duration of treatment were recorded.

Baseline characteristics between phenytoin and sodium valproate group were compared by descriptive statistics. All outcome variables were also tested for the differences between those treated with phenytoin and sodium valproate. Wilcoxon rank sum or student t-test and Fisher’s exact tests or Chi-square test were applied to compare the differences in numbers and proportions between the

| Variables                                | Phenytoin group N = 37 | Sodium valproate N = 17 | p value |
|------------------------------------------|------------------------|-------------------------|---------|
| Age (years)                              | 40 (16–85)             | 42 (16–76)              | 0.852   |
| Male gender (%)                          | 17 (45.95)             | 10 (58.82)              | 0.379   |
| No preexisting condition, N (%)          | 5 (13.51)              | 3 (17.65)               | 0.698   |
| History of epilepsy (%)                  | 6 (16.22)              | 7 (41.18)               | 0.084   |
| Antiepileptic drug withdrawal (%)        | 4 (10.81)              | 5 (29.41)               | 0.121   |
| Admitted to internal medicine ward (%)   | 14 (37.84)             | 6 (35.29)               | 1.000   |
| Generalized tonic clonic seizure type (%)| 37 (100)               | 16 (94.12)              | 0.315   |
| Weight (kg)*                             | 55.5 (40–75)           | 50 (39–97.5)            | 0.343   |
| Time to start treatment (minutes)        | 5 (5–90)               | 10 (5–35)               | 0.127   |
| Independent status prior to SE, N (%)    | 28 (75.68)             | 17 (100)                | 0.177   |
| Laboratory findings                      |                        |                         |         |
| Hematocrit, g/dL*                        | 31 (15.6–45.7)         | 36.5 (26–49.4)          | 0.273   |
| Total white blood cells, cells/mm³*      | 11610 (4100–29700)     | 8965 (1100–14500)       | 0.168   |
| Blood sugar, mg/dL*                      | 127 (37–568)           | 131 (73–251)            | 0.926   |
| Serum creatinine, md/dL*                 | 1 (0.5–6.1)            | 0.9 (0.5–7)             | 0.445   |
| Serum calcium, md/dL*                    | 8.4 (5.3–10.2)         | 8.2 (0.9–10.7)          | 0.976   |
| Serum albumin, g/dL*                     | 3.3 (1.2–7.4)          | 4.0 (2.2–5.1)           | 0.072   |
| ALT, U/L*                                | 30 (5–375)             | 18 (4–165)              | 0.242   |
| AST, U/L*                                | 56 (11–473)            | 25.5 (0.3–2.2)          | 0.115   |
| Creatinine kinase, U/L*                  | 276 (54–1500)          | 174.5 (44–500)          | 0.396   |
| Abnormal CT brain findings*              | 17 (58.62)             | 7 (53.85)               | 1.000   |
| Electroencephalogram, N*                 | 9 (24.32)              | 5 (29.42)               | 0.745   |

Note. Data presented as median (range) or number (percentage). Data in phenytoin or sodium valproate group may not equal to 37 or 17, respectively due to missing data, ALT serum alanine transaminase, AST serum aspartate transaminase, CT computed tomography, * indicates missing data.
two groups where appropriate. The study protocol was approved by the ethics committee on human research of Khon Kaen University (HE541319).

## Results

During the study period, there were 92 patients diagnosed as SE. Of those 37, 17 SE patients received intravenous phenytoin and 20 received intravenous sodium valproate as the first-line treatment. All patients received diazepam 10 mg intravenously as a rescue medication before starting antiepileptic agents if uncontrolled except one patient in the sodium valproate group.

There were no statistically significant differences in the baseline clinical variables between both groups (Table 1). The median age was higher and the median time to start SE treatment was longer in sodium valproate group. The percentages of patients with male gender, epilepsy, and antiepileptic drug withdrawal were also higher in sodium valproate group. EEG was done in 14 patients (25.93%). There were no statistically significant differences, however, in terms of causes and pre-existing conditions of SE in both groups (Table 2). Details of history of AED usage in patients with previous history of epilepsy are provided in Table 3.

The mean doses of AED used in phenytoin and sodium valproate group were 1.95 (SD 0.85) and 1.82 (SD1.01), (p value 0.508). The numbers of patients with two or more AED usage were 10 (27.02%) and 5 (29.41%) in the phenytoin and sodium valproate groups, respectively (Table 4). Details of AED order of usage in each group are shown in Table 5. The average loading dose of phenytoin was 743 (SD 116) mg with the infusion rate of 20.63 (SD 9.54) mg/min, while sodium valproate was given intravenously at average loading dose of 1000 (SD 239.14) mg and an infusion rate of 26.27 (SD 10.76) mg/min. Then, both medications were given intravenously with maintenance doses of 300 mg of phenytoin and 1,200 mg of sodium valproate. The serum phenytoin levels were measured in 16 patients. The average phenytoin level was 25.71 (SD 28.65) mg/dL, while the average sodium valproate level was 36.82 (SD 73.45) mg/dL (calculated from 7 patients).

Regarding the treatment outcomes (Table 6), there was no significant difference between the phenytoin and sodium valproate groups in all outcome variables. The differences of numbers of clinically-controlled seizure, however, was almost reached a statistical significant level (p value = 0.057). The time to seizure control, duration

### Table 2 Causes of status epilepticus (SE) patients treated with intravenous phenytoin or intravenous sodium valproate as the first-line treatment

| Causes                        | Phenytoin group N = 37 | Sodium valproate N = 17 | p value |
|-------------------------------|-------------------------|-------------------------|---------|
| Antiepileptic drug withdrawal | 4 (10.81)               | 5 (29.41)               | 0.121   |
| Sepsis                        | 7 (18.92)               | 0                       | 0.084   |
| Uremia                        | 0                       | 1 (5.88)                | 0.315   |
| Cardiac arrest                | 5 (13.51)               | 2 (11.76)               | 1.000   |
| Alcohol withdrawal            | 1 (2.70)                | 0                       | 1.000   |
| CNS infection                 | 9 (24.32)               | 3 (17.65)               | 0.584   |
| Head injury                   | 2 (5.41)                | 0                       | 1.000   |
| Metabolic causes              | 9 (24.32)               | 1 (5.88)                | 0.105   |
| Others*                       | 10 (27.03)              | 6 (35.29)               | 0.537   |

Note. Data presented as median (range) or number (percentage); *phenytoin group: hypoxic encephalopathy 3, CNS vasculitis 2, epidural hematoma 1, postcraniotomy 1, tuberculous encephalitis 1, venous thrombosis 1, ischemic stroke 1; sodium valproate group: postcraniotomy 2, sagittal sinus thrombosis 1, subarachnoid hemorrhage 1, intracerebral hemorrhage 1, pregnancy with eclampsia.

### Table 3 Antiepileptic drug usage in status epilepticus treated by intravenous phenytoin and intravenous sodium valproate as the first-line treatment

| Phenytoin group | Sodium valproate group |
|-----------------|------------------------|
| 1. Phenytoin     | 1. Sodium valproate     |
| 2. Phenytoin, Phenobarbital | 2. Sodium valproate |
| 3. Phenytoin, Phenobarbital | 3. Phenytoin, Phenobarbital |
| 4. Phenytoin     | 4. Sodium valproate, Phenobarbital |
| 5. Phenytoin, Phenobarbital | 5. Sodium valproate, Phenytoin |
| 6. Phenytoin, Sodium valproate | 6. Topiramate |
| 7. Topiramate    | 7. Topiramate           |

Note. Bold letter indicates status epilepticus from antiepileptic drug withdrawal.

### Table 4 Numbers of antiepileptic drug (AED) used in status epilepticus patients by group

| No. AED | Phenytoin group N = 37 | Sodium valproate group N = 17 |
|---------|------------------------|-------------------------------|
| 1       | 13 (35.14)             | 9 (52.94)                     |
| 2       | 14 (37.84)             | 3 (17.65)                     |
| 3       | 9 (24.32)              | 4 (23.53)                     |
| 4       | 1 (2.70)               | 1 (5.88)                      |

Note. Bold letter indicates status epilepticus from antiepileptic drug withdrawal.
The number of non-dependent patients or death were better in sodium valproate group (p value > 0.05) as shown in Table 6. There were 13 patients who died during the admission; 2 patients in the sodium valproate group. The median hospitalization days of all 13 patients were 9 days (range 3–31 days). Two patients died from acute renal failure and rhabdomyolysis, while the others died from septicemia. No serious cardiovascular event such as hypotension occurred in either group.

Discussion

This study showed that intravenous sodium valproate has non-inferior efficacy to intravenous phenytoin as the first-line treatment of SE. The intravenous sodium valproate group had better outcomes in all five variables (Table 6). Numbers of patients with clinically-controlled seizures was almost statistically significant (p value 0.057). A previous study by the present authors [5] showed that intravenous sodium valproate can control SE better if used as the first-line compared to the second-line treatment (75% vs 35%). Even though some causes or pre-existing conditions such as AED withdrawal induced SE may be easier to control [16], there was no statistical significance between the groups regarding these two factors (Tables 2 and 3).

The most different outcome between intravenous sodium valproate and phenytoin is the number of non-dependent status patients (22.42%). At baseline, patients in sodium valproate group were all independent, while 75.68% in phenytoin group were independent (p value 0.77). After having SE, the functional status at discharge of both groups were decreased (23.53% in sodium valproate group and 21.63% in phenytoin group, p value 0.143). The baseline functional status of patients in sodium valproate group was better phenytoin group (Table 1) but numbers of patients with worsening functional status (Table 6) was higher in phenytoin group (54.05% vs 41.18%, p value 0.559). The results of the number of patients with worsening of functional status at discharge suggested that patients in the sodium valproate group may have better functional outcomes at discharge.

None of the patients died during the seizure attack but the median survival was 9 days. Two patients died from SE related complications or rhabdomyolysis. Both patients were treated with phenytoin. The mortality rate in the sodium valproate group was much lower than phenytoin group (11.76% vs 29.73%; p value 0.189). Note that small numbers of patients in sodium valproate group. A further prospective study is therefore needed to confirm this finding. The non-significant results of all six outcomes are suggesting that sodium valproate was not inferior to phenytoin as the first-line treatment in SE as previously shown by the meta-analysis [1]. These findings are also compatible with a study from Iran with 30 SE patients. Both medications had comparable efficacy but phenytoin caused more non-serious or skin reactions at the injection site (26.7% vs 0%, p value 0.03) [17].

The reason that intravenous sodium valproate was used commonly in the KKU Hospital during the study period is due to a lack of intravenous phenobarbital. There were no serious cardiovascular compromises in patients who received intravenous sodium valproate. This indicated that intravenous sodium valproate is safe and effective to use as the first-line treatment in SE. Previous studies also showed comparable efficacy of intravenous sodium valproate.

### Table 5 Antiepileptic drugs used in status epilepticus patients by orders

| Order of antiepileptic drugs | Phenytoin group N = 37 | Sodium valproate group N = 17 |
|------------------------------|------------------------|------------------------------|
| Rescuer Diazepam 37          | Diazepam 16            |
| First-line                   | Phenytoin 37           | Sodium valproate 17          |
| Second-line                  | Phenytoin 9            | Sodium valproate 7           |
|                             | Phenobarbital 8        | Phenobarbital 1              |
| Third-line                   | Phenobarbital 7        | Phenobarbital 5              |
|                             | Sodium valproate 1     | Sodium thiopental 1          |
| Fourth-line                  | Propofol 1             | Sodium thiopental 1          |

Note. Numbers after each antiepileptic drug indicates number of patients.

### Table 6 Six outcome variables of status epilepticus patients treated by intravenous phenytoin or sodium valproate as the first-line treatment

| Outcomes                      | Phenytoin N = 37 | Sodium valproate N = 17 | p value   |
|-------------------------------|------------------|-------------------------|-----------|
| Seizure controlled, N         | 8 (21.62)        | 8 (47.06)               | 0.057*    |
| Time to seizure controlled    | 30 (20–30)       | 20 (15–40)              | 0.173***  |
| Hospitalization (days)        | 12 (3–109)       | 9 (2–76)                | 0.434***  |
| Non-dependent status, N       | 20 (54.05)       | 13 (76.47)              | 0.143**   |
| Worsening functional status, N| 20 (54.05)       | 7 (41.18)               | 0.559**   |
| Death, N                      | 11 (29.73)       | 2 (11.76)               | 0.189**   |

Note. Data presented as median (range) or number (percentage); p value was calculated by *Chi-square, **Fisher Exact test, or ***Wilcoxon rank sum test.
valproate in SE when compared to intravenous phenytoin [1,17].

There are some limitations to the present study. The retrospective study design had incomplete data collection. The numbers of patients in each group were also not comparable. Phenytoin is recommended as the first-line antiepileptic drug for status epilepticus in Thailand, while sodium valproate may be used in the elderly, patients with cardiovascular risks or hepatitis. Physicians therefore may choose phenytoin more often than sodium valproate. The outcomes, however, were better in the sodium valproate group. The other limitation is small number of patients in each group. In addition, a prospective study comparing intravenous phenytoin and intravenous sodium valproate as the first-line treatment in SE patients is needed to confirm that intravenous sodium valproate can be used as the first-line AED for recommendations in the SE guidelines.

Conclusion
Intravenous sodium valproate is non-inferior to intravenous phenytoin as the first-line treatment in SE with no significant cardiovascular compromises.

Competing interests
The authors declare that they have no competing interests.

Authors’ contributions
ST: designed the study, verified data, interpreted data, and drafted the manuscript. KS: designed the study, analyzed data, and drafted the manuscript. AC: data collection. All authors read and approved the final manuscript.

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References
1. Liu X, Wu Y, Chen Z, Ma M, Su L: A systematic review of randomized controlled trials on the therapeutic effect of intravenous sodium valproate in status epilepticus. Int J Neurosci 2012, 122:277–283.
2. Miro J, Toledo M, Santamarina E, Ricciardi AC, Villanueva V, Pato A, Ruiz J, Juvany R, Falip M: Efficacy of intravenous lacosamide as an add-on treatment in refractory status epilepticus: A multicentric prospective study. Seizure 2013, 22(1):77–79.
3. Hottinger A, Sutter R, Marsch S, Rüegg S: Topiramate as an adjunctive treatment in patients with refractory status epilepticus: an observational cohort study. CNS Drugs 2012, 26(9):761–772.
4. Zelano J, Kamien E, Levetiracetam as alternative stage two antiepileptic drug in status epilepticus: a systematic review. Seizure 2012, 21(4):233–236.
5. Tiamkao S, Sawanyawisuth K: Predictors and prognosis of status epilepticus treated with intravenous sodium valproate. Epileptic Disord 2009, 11(3):228–231.
6. Paknahad Z, Chitsaz A, Zadeh AH, Sheklabadi E: Effects of common anti-epileptic drugs on the serum levels of homocysteine and folic acid. Int J Prev Med 2012, 3(5):856–5190.
7. Lowenstein DH, Allredge BK: Status epilepticus. N Engl J Med 1998, 338:970–976.
8. Naritoku DK, Mueded S: Intravenous loading of valproate for epilepsy. Clin Neuropsychopharmacol 1999, 22:102–106.
9. Uberall MA, Trollmann R, Wunsiedler U, Wenzel D: Intravenous valproate in pediatric epilepsy patients with refractory status epilepticus. Neurology 2000, 54(11):2188–2189.
10. Devinsky O, Leppik I, Willmore LJ, Pellock JM, Dean C, Gates J, Ramsay RE: Safety of intravenous valproate. Ann Neurol 1995, 38(6):670–674.
11. Holte LM, Gadd BE, Collins DM: Valproate in status epilepticus. Ann Pharmacother 1998, 32(10):1042–1044.
12. Venkataraman V, Whelans JW: Safety of rapid intravenous infusion of valproate loading doses in epilepsy patients. Epilepsy Res 1999, 35(2):147–153.
13. Meierkord H, Boon P, Engelsen B, Göcke K, Shorvon S, Tinuper P, Holtkamp M: EFNS guideline on the management of status epilepticus. Eur J Neurology 2006, 13(5):445–450.
14. Treiman D: Convulsive Status Epilepticus. Curr Treat Options Neurol 1999, 1(4):359–369.
15. Meierkord H, Holtkamp M: Non-convulsive status epilepticus in adults: clinical forms and treatment. Lancet Neurology 2007, 6(4):329–339.
16. Neligan A, Shorvon SD: Prognostic factors, morbidity and mortality in tonic-clonic status epilepticus: a review. Epilepsy Res 2011, 95(1):1–10.
17. Chitsaz A, Mehvaran J, Salari M, Gholami F, Najafi M: A comparative assessment the efficacy of intravenous infusion of sodium valproate and phenytoin in the treatment of status epilepticus. Int J Prev Med 2013, 4(Suppl 2):S216–S221.

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