Comparison Efficacy and Safety of Intravenous Push Levetiracetam Vs Midazolam for Seizure Termination in Non-Convulsive Status Epilepticus. A Double-Blind Randomized Controlled Trial

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Abstract

Background: non-convulsive status epilepticus (NCSE) among hospitalized patients results in increased morbidity and mortality. The diagnosis and treatment of NCSE are still challenging in patient care. The role of antiepileptic drug in NCSE has been limited. Therefore, we conducted a trial to investigate the efficacy and safety of levetiracetam compared to midazolam use to treatment of NCSE in hospitalized patients.

Methods: This study was a randomized double blind controlled trial conducted at Thammasat University Hospital, Pathumthani, Thailand. Hospitalized patients aged≥18 years and was met the electroencephalography criteria were randomized to levetiracetam or midazolam group. The primary end point was seizure termination. Secondary end points were time to seizure termination, safety, mrs score at discharge and 90-day mortalities.

Results: A total of 31 patients were enrolled in the study. The patients were included in an intention-to-treat analysis allocated to the levetiracetam (n=15) or midazolam (n=16) group. The seizure termination incidence rates in levetiracetam and midazolam groups were 5 (33.3%) and 12 (75%) (OR=5.4, 95%CI 1.6-9.2, P=0.020), respectively. The time to seizure termination was 10 (8-12) minutes in levetiracetam group and 8 (6-10) minutes in midazolam group, P=0.078. Neither injection site reaction nor unstable vital sign were reported. The median length of hospital stay was 30 (3-123) versus 27 (6-85), P=0.572 respectively. There were no statistically significant number of antiepileptic drugs (AEDs) use 2 (1-3) versus 1 (1-2) respectively; There were no

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statistically significant difference in median functional outcome at discharge in 2 groups.

Conclusion: Treatment of NCSE with midazolam was better in seizure termination when compared to levetiracetam in this population group.

Keywords: Nonconvulsive status epilepticus, Levetiracetam, Midazolam

Background

Non-convulsive status epilepticus (NCSE) refers to a prolong seizure that manifests primarily as altered mental status as opposed to the dramatic convulsions seen in generalized tonic-clonic status epilepticus. Subtle status epilepticus (SSE) is the type of NCSE must be considered in comatose patients who present after a prolong generalized tonic-clonic seizure and who may have only subtle motor manifestations of a seizure, such as facial or hand twitchings. The mortality associated with SSE can exceed 30% if the seizure duration is greater than 60 minutes.[1] Non-convulsive status epilepticus (NCSE) in a comatose patient cannot be diagnosed without electroencephalography (EEG).[2] Salzburg consensus criteria for diagnosis of NCSE were proposed at the 4th London-Innsbruck colloquium on status epilepticus in Salzburg (2013)[3] Midazolam is a standard drug used for guiding a diagnosis of NCSE, possible NCSE[3] During covid-19 era, midazolam was out of stock. Levetiracetam (LEV) is a board-spectrum antiepileptic drug that is effective against a variety of seizure types. Its rapid onset of action, lack of drug-drug interactions and availability as intravenous solution make it an optimal drug to treat NCSE.[4] The rapid administration of undiluted intravenous levetiracetam is safe.[5] Therefore, in our study, we aimed to evaluated the efficacy and safety of levetiracetam compared to midazolam for the treatment of NCSE in hospitalized patients.

Method

Trial design

We conducted a single-center, double-blind, randomized, controlled study at Thammasat University hospital, Pathumthani, Thailand. Participants were recruited between July 2021 and December 2022. The study was approved by the committee of Faculty of Medicine, Thammasat University Hospital. Midazolam and levetiracetam were supplied by the pharmaceutical department of Thammasat University Hospital.

The study carried out the randomization, and blinded the investigators and subjects. An independent data and safety monitoring committee evaluated all potentially serious adverse events. The study was conducted according to the declaration of Helsinki and Good Clinical Practice Guidelines. The study adheres to CONSORT guidelines.

Participants

Eligible participants were patients aged ≥18 years and were diagnosed non-convulsive status epilepticus (NCSE) due to 6 conditions, 1. CNS infection 2. Metabolic derangement 3. Severe systemic infection 4. Ischemic stroke 5. Hypoxia, and 6. Head trauma. Patients or relative provided written informed consent before participation or reconsent after enrollment.

Randomization and interventions

Eligible and consenting patients were randomly assigned to midazolam or levetiracetam intravenous injection. The dosage of midazolam or levetiracetam was based on the recommended dose as patient's body weight.

Midazolam group, 25-50kg=2.5 mg, 50-75 kg=5 mg, 75-100 mg=7.5 mg, 100-125 kg=10 mg intravenous push.

Levetiracetam group, 25-50 kg=750 mg, 50-75 kg=1000 mg, 75-100 kg=1500 mg, 100-125 kg=2000 mg intravenous push.

Patients were randomized into the midazolam or levetiracetam group using fixed randomization schemes per site with a block size of 4 (1:1) according to computer-generated randomization list. The medication was given by the nurse. Study staff, clinicians, and participants were to remain blinded throughout the study.

Exclusion criteria were 1. Pregnant or breast-feeding woman 2. Liver failure 3. Renal failure (creatinine clearance ≤ 30) and 4. Patients who were diagnosed non convulsive status epilepticus from other determined caused exception from inclusion criteria.

Outcomes

The primary outcome was the stop of seizure incidence defined as EEG criteria as the followings;

EEG improvement after intravenous antiepileptic drug

EEG showed termination of seizure and/or increase in prominence of frequency of the features when compared to baseline

Secondary outcomes were time to seizure termination in midazolam and levetiracetam, safety of both drugs (injection site reaction, hemodynamic), mrs score at discharge, and 90-day mortalities.

Data collection

All patients were assessed by trained clinicians and investigators. Baseline demographic and health-related characteristics were recorded. EEG was assessed by experienced clinicians or investigators. Once the patient was diagnosed as non-convulsive status epilepticus (NCSE). EEG was done. A session of EEG assessment based on the following criteria;

1) EEG showed epileptiform discharge ≤2.5/second and

1.1) Typical spatiotemporal evolution

1.2) Subtle clinical ictal phenomenon

1.3) Fluctuation without definite evolution

and/or 2) EEG showed delta, or theta activity ≥0.5/second and

2.1) Typical spatiotemporal evolution

2.2) Subtle clinical ictal phenomenon

2.3) Fluctuation without definite evolution

When above criteria was presented. The blinded randomized drug was administered. A document consisted of a case record form was attacked to the patient's medical chart and filled in by the investigator to monitor and record the outcomes.

Sample size

Sample size was calculated based on the assumptions that the incidence of EEG and clinical outcome after receiving midazolam was 16.2%[3] EEG and clinical outcome after receiving levetiracetam was 56.2%.[6] To detect a significant difference between groups, we sought to randomized 54 patients into 2 groups of 27 patients per treatment arm to give 80% significant power at a two-side 5% significant level (alpha). However, this study was randomized 31 patients, 16 patients into midazolam group and 15 patients into levetiracetam group. The protocol was early terminated because of the result of preliminary analysis was significant different of the midazolam efficacy when compared to levetiracetam and we concern about patients safety.

Table 1 Baseline characteristic of total study population (intention-to-treat)

	Midazolam (n=16)	Levetiracetam (n=15)	All (n=31)	p-value
Male, n (%)	10 (62.5%)	7(46%)	17 (54.8%)	
Female, n (%)	6 (37.5%)	8 (54%)	14 (45.1%)	0.376
Age, median (IQR)	62 (56-77)	76 (50-85)	68 (56-77)	0.922
BW(kg) , mean (SD)	68.31 (12.57)	76.00 (9.10)	72 (11.53)	0.367
Indication for admission				
CNS infection, n (%)	3 (18%)	1 (6.6%)	4 (12.9%)	0.083
Metabolic derangement, n (%)	7 (43.7%)	4 (26.6%)	11(35.4%)	0.320
Severe systemic infection, n (%)	0 (0%)	1 (6.6%)	1 (3.2%)	0.294
Ischemic stroke, n (%)	5 (31.2%)	2 (13.3%)	7 (22.5%)	0.233
Hypoxia, n (%)	1 (6.2%)	0 (0%)	1 (3.2%)	0.325
Head trauma, n (%)	0 (0%)	7 (46.6%)	7 (22.5%)	0.002
State of consciousness				
Alert, n (%)	2 (12.5%)	2 (13.3%)	4 (12.9%)	0.945
Drowsy, n (%)	11 (68.7%)	10 (66.6%)	21 (67.7%)	0.901
Stupor, n (%)	3 (18.7%)	2 (13.3%)	5 (16.1%)	0.682
Coma, n (%)	0 (0%)	1 (6.6%)	1 (3.2%)	0.294
History of previous AED medication, n (%)	1 (6.2%)	3 (20%)	4 (12.9%)	0.254
Underlying disease				
Chronic kidney disease, n (%)	8 (50%)	4 (26.6%)	12 (38.7%)	0.183
Diabetes mellitus type2, n (%)	6 (37.5%)	6 (40%)	12 (38.7%)	0.886
Underlying disease				
Essential hypertension, n (%)	12 (75%)	10 (66.6%)	22 (70.9%)	0.609
Dyslipidemia, n (%)	6 (37.5%)	5 (31.2%)	11 (35.4%)	0.809
Ischemic heart disease, n (%)	5 (31.2%)	0 (0%)	5 (16.1%)	0.018
Ischemic stroke	3 (18.7%)	2 (13.3%)	5 (16.1%)	0.682

Table 2 Study outcome (intention-to-treat)

outcome	Midazolam (n=16)	Levetiracetam (n=15)	OR or difference (95%CI)	p-value
Primary outcome				
Seizure termination, n (%)	12 (75%)	5 (33.3%)	5.4 (1.6-9.2)	0.020
Secondary outcome				
Time to seizure termination, (minutes)	8 (6-10)	10 (8-12)	2 (1-3)	0.078
Injection site termination				
No skin reaction, n (%)	16 (100%)	15 (100%)	0	-
Warmth, redness, tender at injection site, n (%)	0 (0%)	0 (0%)	0	-
Hemodynamic recording				
Stable vital sign, n(%)	16 (100%)	15 (100%)	0	-
Unstable vital sign, n (%)	0 (0%)	0 (0%)	0	-
Length of stay (day), median (IQR)	27 (6-85)	30 (3-123)	3 (1-5)	0.572
Number of AEDs	1 (1-2)	2 (1-3)	1 (0-1)	0.232

Table 2 Study outcome (intention-to-treat) (cont.)

outcome	Midazolam (n=16)	Levetiracetam (n=15)	OR or difference (95%CI)	p-value
Anesthetic agent uses, n (%)	0 (0%)	0 (0%)	0	-
Functional outcome (mrs score) at discharge				
1	5 (31.25%)	1 (6.6%)		0.012
2	0 (0%)	0 (0%)		-
3	0 (0%)	1 (6.6%)		0.294
4	8 (50%)	7 (46.6%)		0.853
5	0 (0%)	1 (33.3%)		0.294
6	3 (18.7%)	5 (33.3%)		0.354
Median functional outcome (mrs score) at discharge	3 (2-4)	4 (3-5)	1 (0-1)	0.163

Table 3 Sensitivity analysis

outcome	Midazolam (n=16)	Levetiracetam (n=15)	OR or difference (95%CI)	Interaction effect p-value
State of consciousness group				
Alert	N=2	N=2		
Seizure termination, n (%)	2 (100%)	0 (0%)	2 (1.1-5.3)	0.013
Drowsy	N=11	N=10		
Seizure termination, n (%)	7 (63%)	5 (50%)	2.3 (1.4-3.8)	0.002
Stupor	N=3	N=2		
Seizure termination, n (%)	1 (33.3%)	0 (0%)	1.25 (1-1.9)	0.002
Coma	N=0	N=1		
Seizure termination, n (%)	0 (0%)	0 (0%)	0	-
Number of AEDs				
1, n (%)	8 (50%)	4 (26.6%)		0.183
2, n (%)	6 (37.5%)	7 (46.6%)		0.605
3, n (%)	1 (6.25%)	4 (26.6%)		0.122
4, n (%)	1 (6.25%)	0 (0%)		0.325
Seizure termination	12 (75%)	3 (37.5%)	3.2 (0.3-4.6)	0.074
Exclusion of head trauma				

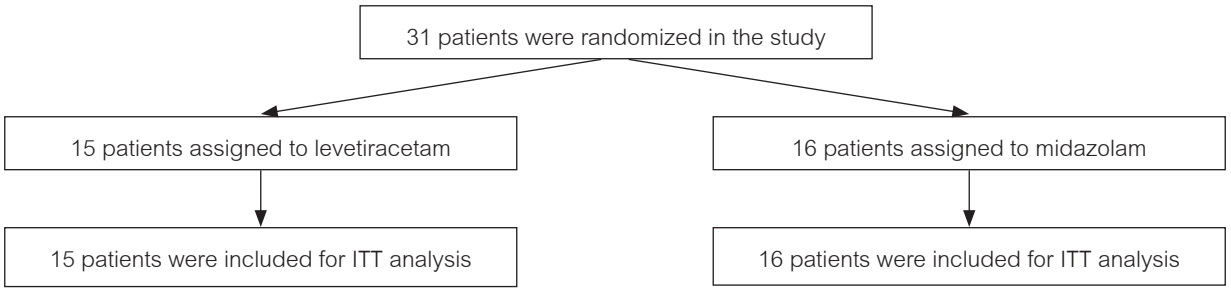
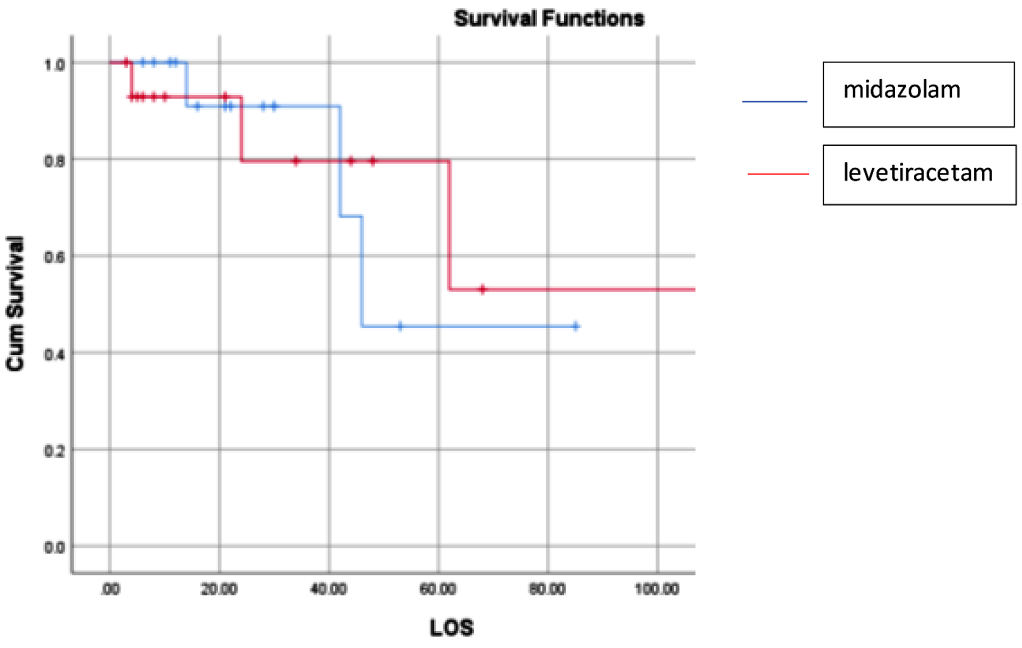


Figure 1 Study flow diagram



Hazard ratio (95%CI) = 1.204 (0.234-6.199), P-value= 0.825

Figure 2 Survival analysis

Statistical analysis

Statistical analyses were performed using IBM SPSS statistics version 25. Descriptive statistics [mean ±standard deviation (SD)], frequency and percentage, or median and interquartile range (IQR) were used to describe baseline patient characteristics. Intention to treat (ITT) analysis was performed.

The incidence of seizure termination was based on EEG outcome. The incidence of seizure termination was completed between groups using the chi-square test. Odd ratio (ORs) with 95% confidence interval (CIs) were reported as effect size using midazolam as a reference group. Secondary outcomes were compared by using the chi-square test or Fisher's exact test for dichotomous and nominal outcomes, the Mann-Whitney U-test for ordinal outcomes and continuous outcomes that were not normally distributed and the Hodges-Lehmann estimator for confidence intervals for the difference between 2 medians. P-values <0.05 were considered statistically significant. Survival analyses presented by Kaplan-Meier curves were used for graphical demonstration. Cox-proportional hazard regression analyses were performed to estimate the hazard ratio (HRs) for survival function of the levetiracetam and midazolam groups.

Sensitivity analyses

Sensitivity analyses were performed with state of consciousness and number of antiepileptic drug use. State of consciousness groups were stratified by alert, drowsy, stupor and coma. Number of epileptic drug use groups were stratified by 1,2,3 and 4.

Results

Enrollment and baseline data

From July 2021 to December 2022, 31 eligible patients were randomly assigned to levetiracetam (n=15) or midazolam (n=16). A total of 31 participants

were included for ITT analysis of the primary outcome. Eight participants (5 in levetiracetam, 3 in midazolam) died during admission. The baseline characteristics of levetiracetam and midazolam groups were not significantly different, except for head trauma as an indication of admission was more in levetiracetam group as demonstrated in Table 1.

Primary outcome

The incidence of seizure termination in the levetiracetam group was 33.3%, while that in the midazolam group was 75% (OR=5.4, 95%CI 1.6-9.2, P=0.020). (Table 2)

Secondary outcome

The median durations of time to seizure termination in the levetiracetam and midazolam group were 10 (8-12) minutes and 8 (6-10) minutes respectively, difference=2 minute (95%CI 1-3). There was no injection site reaction in two group. The hemodynamic was stable in two groups. The median length of stay in the levetiracetam was 30 days (3-123), while that in the midazolam group was 27 days (6-85), P=0.572. The number of AEDs use were not significant different between the two groups, which involved 1 (1-2) in midazolam group and 2.0 (1-3) in levetiracetam group, difference=1 (95%CI 0-1), P=0.232. The median functional outcome at discharge were not significantly different between the two groups (Table 2), survival analyses showed no difference between the levetiracetam and midazolam groups, HR 1.20 (95%CI 0.23-6.19) P=0.825 for 90-day survival.

Subgroup analysis

Sensitivity analyses were performed according to state of consciousness and number of AEDs. We found that when the state of consciousness was alert, drowsy and stupor, seizure termination was significantly increased in midazolam group (Table 3). However, the number of AEDs use were not statistically significant difference in 2 groups (Table 3). Head traumas increase inflammatory marker, altered blood brain barrier, change in astrocyte and glucose metabolism dysregulation in levetiracetam group might effect outcome, so we excluded a patients with head trauma in levetiracetam group, however the seizure termination was 12 (75%) in midazolam group and 3 (37.5%) in levetiracetam group, OR=3.2 (95%CI 0.3-4.6), p-value 0.074

Discussion

In our study, a randomized, double-blind, controlled trial, we found no positive outcome on seizure termination incidence in patients admitted to Thammasat University Hospital assigned to levetiracetam group when compared to midazolam group.

Nonetheless, our study had some limitations. First, we strict to inclusion criteria. We found that the patient diagnosed as intracerebral hemorrhage of any cause (hypertensive hemorrhage, tumor bleeding) had high incidence of non-convulsive status epilepticus (NCSE), but these patients had not been included in the study.

Second, the dosage and administration of the intervention drug might influence the results. In this study, we administered a dosage of levetiracetam and midazolam as a body weight range. Perhaps, the dosage per kilograms might have more accurately result.

Finally, only 31 participants from 54 patients enrolled to this study. Therefore, we could not reach statistical power from our expected sample calculation.

This study demonstrates a benefit for midazolam use when compared to levetiracetam in patient diagnosed as non-convulsive status epilepticus (NCSE). Further trials focusing on different type of antiepileptic drugs with various dosage and administration methods should be conducted. The study population might be narrowed down to one specified disease with similar comorbidities or stratified into disease categories and severities to see potential effect of the medication within different patient groups.

Conclusion

Our study demonstrated that midazolam was effective than levetiracetam on termination of seizure in non-convulsive status epilepticus (NCSE) patient. The length of hospital stay, time to seizure termination, number of AEDs uses, anesthetic uses, functional outcome at discharge were not significantly different between the levetiracetam and midazolam groups. Levetiracetam and midazolam were safe. There were no report of skin reaction nor unstable vital sign.

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