Current Therapeutic Research 95 (2021) 100648

Contents lists available at ScienceDirect

Current Therapeutic Research

journal homepage: www.elsevier.com/locate/curtheres

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

Preechaya Ruangritkul, MSc[1], Siriporn Tiamkao, MD[2,3,*], Nanthaphan Chainirun, MSc[1,3], Sineenard Pranboon, MSc[3,4], Somsak Tiamkao, MD[3,5], Kittisak Sawanyawisuth, MD[5], Sittichai Khamsai, MD[5]

[1] *Pharmacy Department, Srinagarind Hospital, Khon Kaen University, Khon Kaen, Thailand*
[2] *Department of Pharmacology, Faculty of Medicine, Khon Kaen University, Khon Kaen, Thailand*
[3] *Integrated Epilepsy Research Group, Khon Kaen University, Khon Kaen, Thailand*
[4] *Nursing Division, Srinagarind Hospital, Khon Kaen University, Khon Kaen, Thailand*
[5] *Department of Medicine, Faculty of Medicine, Khon Kaen University, Khon Kaen, Thailand*

ARTICLE INFO

Article history:
Received 11 May 2021
Accepted 10 October 2021

Key words:
acute repetitive convulsive seizures
postoperative seizures
status epilepticus
vomiting

ABSTRACT

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) (Focale; 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%; 88.37% 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.

(*Curr Ther Res Clin Exp*. 2022; 83:XXX–XXX)

Introduction

There are 3 main epileptic conditions in hospital settings that may require intravenous antiepileptic drug (AED) treatment: status

* Address correspondence to: Siriporn Tiamkao, MD, Department of Pharmacology, Faculty of Medicine, Khon Kaen University, Khon Kaen, Thailand 40002.
E-mail address: tisirip@kku.ac.th (S. Tiamkao).

https://doi.org/10.1016/j.curtheres.2021.100648

Table 1
clinical parameters of adult patients who received intravenous levetiracetam (Focale®) categorized by indications (n = 93).

Factors	ARCS n = 39	SE n =9	Postoperative n =45	p value
Mean (SD) age, years	43.35 (10.97)	46.00 (6.51)	48.32 (12.97)	0.818
Male sex	21 (53.85)	5 (55.56)	16 (35.56)	0.190
Glomerular filtration rate (GFR)				0.335
GFR > 80 ml/min/1.73m^2	29 (74.36)	7 (77.78)	34 (75.56)	
GFR 50-80 ml/min/1.73m^2	8 (20.51)	1 (11.11)	8 (17.78)	
GFR 30-50 ml/min/1.73m^2	1 (2.56)	1 (11.11)	-	
GFR <30 ml/min/1.73m^2	-	-	3 (6.67)	
ESRD with dialysis	1 (2.56)	-	-	
History of epilepsy	22 (56.41)	5 (55.56)	8 (17.78)	< 0.001
Order of treatment				0.093
First line	29 (74.39)	5 (55.56)	39 (86.67)	
Second line	8 (20.51)	3 (33.33)	6 (13.33)	
Third line	2 (5.13)	1 (11.11)	-	
Mean (SD) of loading dose, mg	1134 (371)	1166 (353)	827 (260)	< 0.001

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

epilepticus (SE), acute repetitive convulsive seizures (ARCS), and postoperative seizures.[1] Levetiracetam (LEV) is a new AED that has low protein binding (<10%).[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.[3] Finally, LEV is reported to be more effective at seizure control in patients with SE compared with phenytoin.[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 individuals with a good quality of life compared with the name-brand LEV.[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,[8–10] only 1 randomized controlled trial evaluated generic IV LEV versus brand-name IV LEV.[11] Both generic and brand-name IV LEV had comparable effects.[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 Stata 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

Table 2
clinical outcomes and managments of adult patients who received intravenous Levetiracetam (Focale®) categorized by indications (n = 93).

Factors	ACRS n = 39	SE n = 9	Postop n = 45	p value
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)	-	0.067
Reloading	4 (10.26)	0	1 (2.22)	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 (17.95)	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.

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/1.73m^2	7 (70.00)	63 (75.90)	0.704
Order of Focale®			0.569
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			0.125
ARCS	7 (70.00)	32 (38.55)	
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 (373.36)	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 33.73%; $P = 0.037$). 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).

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

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/1.73m^2	58 (76.32)	12 (70.59)	0.700
Order of Focale®			0.194
1st line	62 (81.58)	11 (64.71)	
2nd line	12 (15.79)	5 (29.41)	
3rd line	2 (2.63)	1 (5.88)	
Treatment indications			0.231
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.

than monotherapy if a history of epilepsy was present (63% vs 37%).[15]

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.[16,17] 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.

Author's contribution

Preechaya Ruangritkul: study design, literature search, data collection, data interpretation, and writing. **Siriporn Tiamkao:** study design, literature search, data collection, data interpretation, and writing. **Nanthaphan Chainirun:** study design, literature search, data collection, data interpretation, and writing. **Sineenard Pranboon:** literature search, and data interpretation, and writing. **Somsak Tiamkao:** literature search, and data interpretation, and writing. **Kittisak Sawanyawisuth:** literature search, data analysis, and data interpretation, and writing. **Sittichai Khamsai:** literature search, and data interpretation, and writing.

Acknowledgments

This study was funded by the Great Eastern Drug Company, which provided the studied medications for all patients but was not involved in any other aspect of the study (including study design, data collection, data analysis, presentation of results, or manuscript preparation).

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.

References

1. Limotai C, Boonyapisit K, Suwanpakdee P, et al. From international guidelines to real-world practice consensus on investigations and management of status epilepticus in adults: A modified Delphi approach. *J Clin Neurosci*. 2020;72:84–92. doi:10.1016/j.jocn.2020.01.008.
2. Fuller KL, Wang YY, Cook MJ, et al. Tolerability, safety, and side effects of levetiracetam versus phenytoin in intravenous and total prophylactic regimen among craniotomy patients: a prospective randomized study. *Epilepsia*. 2013;54(1):45–57. doi:10.1111/j.1528-1167.2012.03563.x.
3. Zaccara G, Franciotta D, Perucca E. Idiosyncratic adverse reactions to antiepileptic drugs. *Epilepsia*. 2007;48(7):1223–1244. doi:10.1111/j.1528-1167.2007.01041.x.
4. Gujjar AR, Nandhagopal R, Jacob PC, et al. Intravenous levetiracetam vs phenytoin for status epilepticus and cluster seizures: A prospective, randomized study. *Seizure*. 2017;49:8–12. doi:10.1016/j.seizure.2017.05.001.
5. Vari MS, Pinto F, Mencaroni E, Giudizioso G, Minetti C, La Neve A, Francavilla T, Piccioli M, Striano S, del Gaudio L, Tovo P, Striano P, Verrotti A. Safety of Overnight Switch from Brand-Name to Generic Levetiracetam. *Clin Drug Investig*. 2016 Jan;36(1):87–91 PMID: 26507620. doi:10.1007/s40261-015-0351-1.
6. Olsson P, Reimers A, Källén K. Quality of life after switching to generic levetiracetam - A prospective comparative study. *Epilepsy Behav*. 2019 Jul;96:169–174 Epub 2019 May 28. PMID: 31150996. doi:10.1016/j.yebeh.2019.04.029.
7. Olsson P, Reimers A, Källén K. Quality of life after switching to generic levetiracetam - A prospective comparative study. *Epilepsy Behav*. 2019 Jul;96:169–174 Epub 2019 May 28. PMID: 31150996. doi:10.1016/j.yebeh.2019.04.029.
8. Nakamura K, Inokuchi R, Daidoji H, Naraba H, Sonoo T, Hashimoto H, Tokunaga K, Hiruma T, Doi K, Morimura N. Efficacy of levetiracetam versus fosphenytoin for the recurrence of seizures after status epilepticus. *Medicine (Baltimore)*. 2017 Jun;96(25):e7206 PMID: 28640109; PMCID: PMC5484217. doi:10.1097/MD.0000000000007206.
9. Chamberlain JM, Kapur J, Shinnar S, Elm J, Holsti M, Babcock L, Rogers A, Barsan W, Cloyd J, Lowenstein D, Bleck TP, Conwit R, Meinzer C, Cock H, Fountain NB, Underwood E, Connor JT, Silbergleit R. Neurological Emergencies Treatment Trials; Pediatric Emergency Care Applied Research Network investigators. Efficacy of levetiracetam, fosphenytoin, and valproate for established sta-

tus epilepticus by age group (ESETT): a double-blind, responsive-adaptive, randomised controlled trial. *Lancet*. 2020 Apr 11;395(10231):1217–1224 Epub 2020 Mar 20. PMID: 32203691; PMCID: PMC7241415. doi:10.1016/S0140-6736(20)30611-5.
10. Nakamura K, Marushima A, Takahashi Y, Kimura A, Asami M, Egawa S, Kaneko J, Kondo Y, Yonekawa C, Hoshiyama E, Yamada T, Maruo K, Inoue YIENE ECT with the LIFE study group. Levetiracetam versus fosphenytoin as a second-line treatment after diazepam for status epilepticus: study protocol for a multicenter non-inferiority designed randomized control trial. *Trials*. 2021 May 2;22(1):317 PMID: 33934714; PMCID: PMC8091776. doi:10.1186/s13063-021-05269-7.
11. Wongjirattikarn R, Sawanyawisuth K, Pranboon S, et al. Can Generic Intravenous Levetiracetam Be Used for Acute Repetitive Convulsive Seizure or Status Epilepticus? A Randomized Controlled Trial. *Neurol Ther*. 2019;8(2):425–431. doi:10.1007/s40120-019-00150-x.
12. Hocker SE, Britton JW, Mandrekar JN, et al. Predictors of outcome in refractory status epilepticus. *JAMA Neurol*. 2013;70(1):72–77. doi:10.1001/jamaneurol.2013.578.
13. Horváth L, Fekete I, Molnár M, et al. The Outcome of Status Epilepticus and Long-Term Follow-Up. *Front Neurol*. 2019;10:427. doi:10.3389/fneur.2019.00427.
14. Shorvon S. The management of status epilepticus. *J Neurol Neurosurg Psychiatry*. 2001;70(Suppl 2):II22–II27 Suppl 2. doi:10.1136/jnnp.70.suppl_2.ii22.
15. Rossetti AO, Logroscino G, Bromfield EB. Refractory status epilepticus: effect of treatment aggressiveness on prognosis. *Arch Neurol*. 2005;62(11):1698–1702. doi:10.1001/archneur.62.11.1698.
16. Ogunsakin O, Tumenta T, Louis-Jean S, et al. Levetiracetam Induced Behavioral Abnormalities in a Patient with Seizure Disorder: A Diagnostic Challenge. *Case Rep Psychiatry*. 2020 2020. doi:10.1155/2020/8883802.
17. Esang M, Santos MG, Ahmed S. Levetiracetam and Suicidality: A Case Report and Literature Review. *Prim Care Companion CNS Disord*. 2020;22(4) 19nr02502. doi:10.4088/PCC.19nr02502.
18. Newsome SD, Xue LY, Jennings T, et al. Levetiracetam-induced diffuse interstitial lung disease. *J Child Neurol*. 2007;22(5):628–630. doi:10.1177/0883073807302602.
19. Sawunyavisuth B. What are predictors for a continuous positive airway pressure machine purchasing in obstructive sleep apnea patients? *Asia Pac J Sci Technol*. 2018;23 APST-23-03-10doi.org/. doi:10.14456/apst.2018.10.
20. Jingmark S, Kuhirunyaratn P, Theeranut A, et al. Subjective well-being and related factors among community-dwelling elderly in Udon Thani Province, Thailand. *Asia Pac J Sci Technol*. 2020;25 APST-25-01-09.
21. Kingkaew N, Antadech T. Cardiovascular risk factors and 10-year CV risk scores in adults aged 30-70 years old in Amnat Charoen Province, Thailand. *Asia Pac J Sci Technol*. 2019;24 APST-24-04-04.