Original Article

How to Expedite Antiepileptic Medications for Status Epilepticus and Acute Seizure Patients

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Background: Status Epilepticus (SE) is one of the major health problems that require immediate treatment to avoid risk of disability and death. The key treatment is to stop the symptom within an hour after it has developed. The problems of SE treatments are mostly caused by delayed diagnosis, incorrect prescription, incorrect rate of administration, inappropriate dilution of medicines.

Objective: In order to provide efficient treatment and reduce the waiting time. The multidisciplinary team, under the lead of Integrated Epilepsy Research Group, has developed a ready-to-use Status Epilepticus Box (SE Box) for status epilepticus and the acute seizure at Srinagarind Hospital.

Materials and Methods: A ready-to-use SE Box comprises of 4 medicines; phenytoin, phenobarbital, sodium valproate, and levetiracetam encloses with information on application of each medicine. The boxes are prepared by pharmacist. Nurses can immediately use antiepileptic drug follow doctors' prescriptions.

Results: The review of seizure patients' records showed an average diagnosis time was 154.77 minutes (1 to 53 hours), an average time of medical receiving was 41.74 minutes (1 to 150 minutes). The average waiting time for receiving medicine in pharmacy department was 13.09 minutes, start from raising order by doctors to the medicine dispensing. SE Box can reduce the waiting time in pharmacy department to zero. Following a doctor's approval, nurses can administer the medicine to the patients by following the instructions available in SE Box. The instructions include loading dose, maintenance dose, administer rate, preparing method, and precautions.

Conclusion: The development of anti-seizure medical system in Srinagarind Hospital, Khon Kaen University, has resulted in the production of the SE Box, an innovation that is efficient in reducing the waiting time prior to applying medication to the patients. The SE Box is ready and convenient for use.

Keywords: Status Epilepticus, Refractory Status Epilepticus, Status Epilepticus Drug Box (SE Box)

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Since Status Epilepticus (SE) is an emergency sickness affecting the primary nerve system that can be life-threatening for the patients, it is crucially important for the sickness to be quickly addressed and treated[(1)]. The International League Against Epilepsy (2015)[(2)] defines SE as a seizure that lasts longer than 30 minutes or the fluctuating seizure of longer than 30 minutes, both involving the patients' unconsciousness. The occurrence of the incidence in Asia is portrayed at a ratio of 42: 100,000 people per year[(3)] and the number is 5: 100,000 people per year[(4)]. In general, the seizure can occur and stop within 2 to 3 minutes. In SE, however, the symptom may continually persist between 5 to 10 minutes or longer due to the descending of post-synaptic GABA-A receptor and the escalading of post-synaptic glutamatergic. This conversing reaction results in the malfunctioning of synaptic inhibition, and the inactiveness of GABA-A receptor on GABA-A being released from pre-synaptic (desensitization). The continuity of this malfunctioning portends to the existence of seizure. Given that the seizure is left without a timely treatment within the first hour of existence, human body will lose its ability to subside the seizure on its own due to damage by the seizure on; the continual reduction of GABA-A receptor and desensitization, the transition of some GABA-A receptor subunits around synapse (trafficking of GABA-A receptors). Other abnormalities triggered by seizure are the over-expansion of P-glycoprotein around hippocampus and cortex, the reduction of GABA-A subunit Alpha 1,2,3,4,5, Beta 2/3 and Gamma 2. This body process against seizure is reducing it, adversely,

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the factors portending for seizure are advocated under the continual and untreated seizure. This conversing reaction can be so severe that the neuronal injury and neuronal death can be developed, which can be finalized as RSE causing death among the patients due to metabolic acidosis and rhabdomyolysis and infection[5,6].

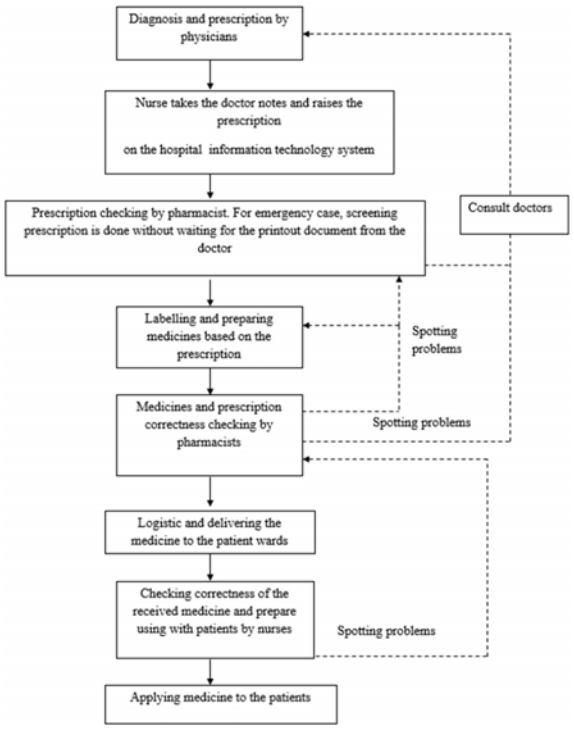
As referred to in a study by Tsai et al[7], SE newly developed in a group of 83 patients was a result of a constant and severe brain injury and none of the patients had a previous record of seizures. However, it was reported in a study by Aminoff that the cause of a seizure investigated among the chronic patients was found to be related to the patient's negligence of the doctor's advice on the use of medicine. The cause of seizure in Thailand is mostly associated with the brain injury as mentioned in Tsai et al[7]. Other factors that portend to RSE development are: patients suffering from meningo encephalitis, hypoxic-ischemic encephalopathy and sepsis; patients experiencing longer than 24 hours seizure, patients suffering non-convulsive SE, and patients above 65 years old[8].

Based on the knowledge on the mechanism of SE, RSE and medical resistance, it is required that these symptoms and their supporting factors be eliminated urgently. The main attributor of RSE is a long time it takes to wait for the treatment. Anti-seizure medicine should be prescribed constantly following the doctor's diagnosis, while it is equally important for the medical description to be performed strictly throughout the course of the treatment[5]. Based on Clinical Guidelines for Epilepsy 2016[1], the on-service doctors are advised to prescribe the following medicines for different phases of seizure; Early Stage (first 5 to 10 minutes of seizure): Benzodiazepine Group (intravenous diazepam and intramuscular midazolam), Established Stage (10 to 30 minutes of seizure): Antiepileptic Group (phenytoin, phenobarbital, sodium valproate and levetiracetam) and Refractory Stage (30 to 60 minutes): midazolam, propofol, thiopental, ketamine.

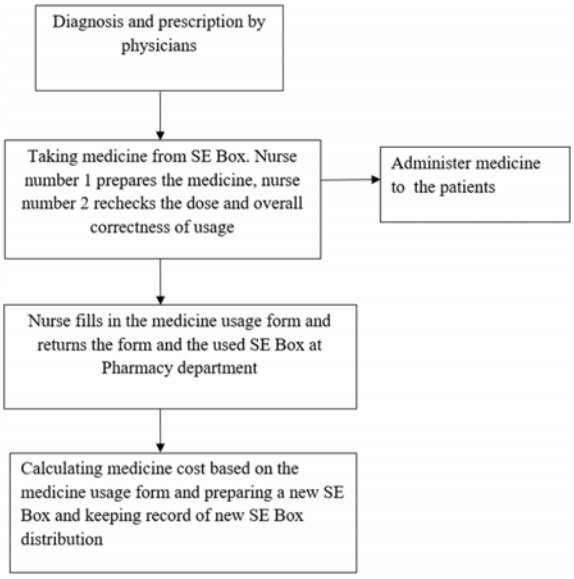
The medical receiving procedure of Srinagarind Hospital starts from physician diagnosis and doctor's prescription, processing online prescription system, processing of the prescription by pharmaceutical assistants, screening drug based on the prescription, checking the correctness of the prescribed drug by pharmacists, transporting the drug to the patient wards. The researcher is aware of the need to provide a prompt treatment to prevent casualty among the patients while confident that many procedures of medicine obtaining can be removed to ensure faster health service for the patients suffering SE. This research was conducted in order to develop an medical injection system to help subside symptoms of SE and acute seizure among the patients in Srinagarind Hospital while effectively shorten the time for the patients to obtain the medicine.

Research methodology

This descriptive research involved the reviewing of the medical records of the patients experiencing SE to obtain data relating to the patients' waiting time for medicine



Conventional procedures to obtain seizure medicine (before the introduction of SE box).



Procedures to obtain seizure medicine with SE Box.

obtaining. The data collection period started from January 1st to December 31st, 2017. The reasons to why delayed medical treatment was performed on the seizure patient were investigated. Data obtained from small group discussion among the members of the Integrated Epilepsy Research Group were incorporated into the designing of the SE Box, a

ready for use medical package for SE and acute seizure treatment. The medical treatments of a seizure are divided into three groups in correspondence with the seizure's phases, each is prescribed with particular medicines. Early Stage (first 5 to 10 minutes of seizure) is treated by medicines in the benzodiazepine Group; intravenous diazepam and intramuscular midazolam. These medicines for early state of seizure are stored at the patient wards; therefore, they are not included in the SE Box. The seizure medical package contains medicines for the Established Stage (10 to 30 minutes of seizure), which are medicines in antiepileptic Group; phenytoin, phenobarbital, sodium valproate and levetiracetam. Since the main purpose of the SE Box is to ensure that the medicine is used promptly for the patients undergoing seizure, the medicines included in the SE Box are accordingly packed based on the medical loading dose. It is worth noting, however, that the medicines to be used continually are obtained based on a conventional method of medicine distribution as ruled by Srinagarind Hospital.

After the calculation of loading dose, the following medicines are included in the package of SE Box; 6 vials of Phenytoin injection, 5 ampules of Phenobarbital injection, 6 vials of sodium valproate injection and 8 vials of levetiracetam injection. Listed below are reference Loading dose (LD)[9-13] of the medicines included in SE Box.

- Phenytoin: Dose LD 20 to 30 mg/kg (maximum dose 1,500 mg).
- Phenobarbital Dose LD 20 to 30 mg/kg (maximum dose 1,000 mg)
- Sodium valproate Dose LD 20 to 30 mg/kg (maximum dose N/A).
- Levetiracetam Dose LD 30 to 40 mg/kg (maximum dose 4,000 mg).

Based on the review of medical information of the pharmacy department in 2017, there were 17 questions that mentioned the use of medicine against seizure. These questions were about stability and administration of drugs, dosage and methods of treatment, undesirable side effects of the drugs. In order to answer these questions, the pharmacists traditionally have to search for the answer from the database, which is quite time-consuming. Therefore, the researcher has developed a complete manual for the application of all of the medicines included in the SE Box as illustrated in Figure 1. The information of the medicine includes; medicine's form of usage and dose, usage indicators, medicine administration, undesirable side effects, symptoms needed to be reported to doctors, and antidotes. The availability of these data helps the physicians to quickly use the medicines to subside seizure and reduce the rate of refractory SE.

The wards that are equipped with the SE Box (Figure 2) are the ICU and the Semi ICU that have to most frequently hospitalize seizure patients including;, IMC4B, 4C, 4A, AE1, AE2, AE3, AE4, MICU1, MICU2, CCU, NSICU, IMC3C, SICU, S & EICU. The pharmaceutical room takes the records of; the SE Box number and its designated patient room at which the SE Box is used, the expiration dates-the medicine with the most-early expiration is labeled on the SE Box to ensure that no expired medicine is used. The usage of SE Box is kept on the medical record to keep the history of medical withdrawal from the SE Box. All of these recording processes are under pharmacists' monitoring.

Following a doctor's approval, the on-duty nurses can process the medicine in the SE Box. The first nurse should be responsible for preparing the medicine and the second nurse rechecks the preparation and fills the medicine usage form before using the drug with the patients as shown

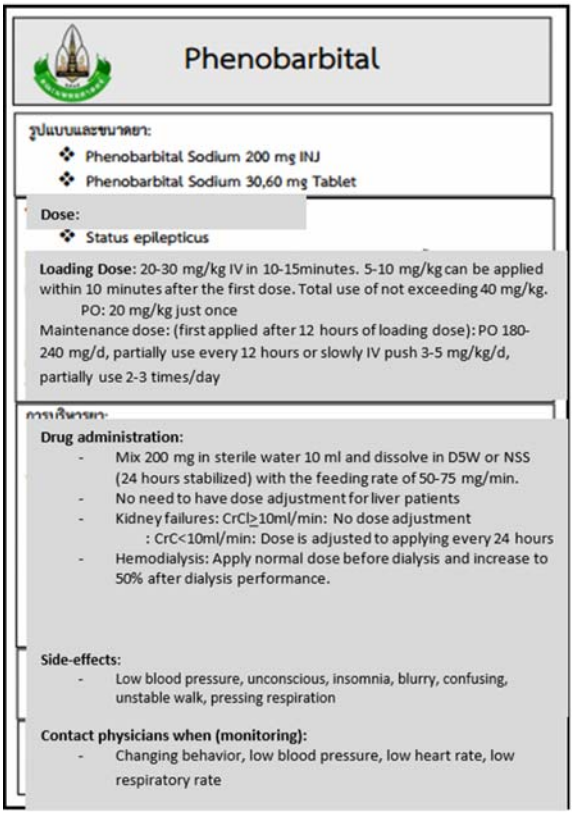


Figure 1. Example of labelling in SE Box for Phenobarbital.

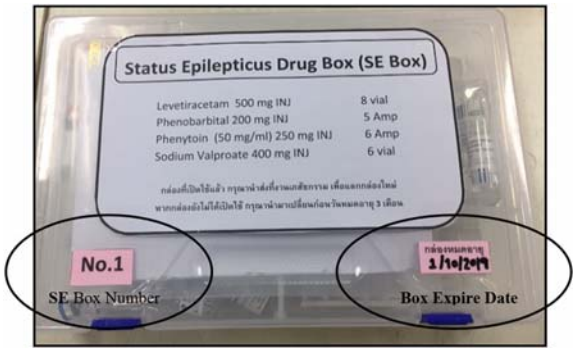


Figure 2. Status Epileptic Box (SE Box).

in Figure 4. Data in the medicine usage form includes; the patient's data, list of medicines and the recorded amount of real usage. The nurses are obliged to always present the SE Box record and the used SE Box to the Medicine Room to calculate the medical cost and have a new SE Box replacement. The pharmacist calculates the medicine cost and rechecks the price with the remaining medicine before dispensing of a new SE Box to the patient wards.

It is obvious that the application of SE Box makes it possible for the patients to receive the medicine soon after the doctor's prescription. It supersedes the traditional practice among the nurses in raising the doctor's prescription on the hospital database. SE Box is capable of reducing tasks in the Pharmaceutical Room at which the practices of allotting the medicine based on the prescription and drug dispensing are removed. Moreover, the patient's time to wait for medicine logistic system is minimized, the error due to wrong medical use is prevented via the application of two nurses for the medical usage, at which the first nurse takes care of drug preparation and another for rechecking the prepared medicine prior to its actual application to the patients. The

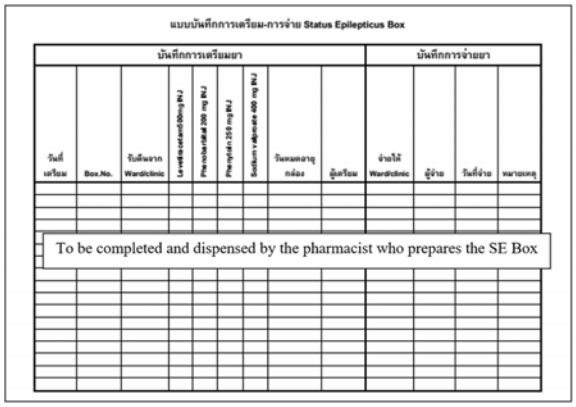


Figure 3. Dispensing record of SE Box.

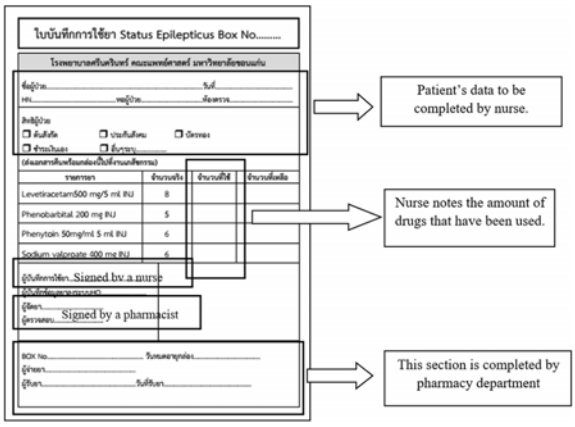


Figure 4. Record of Medical Use in SE Box.

SE Box's ability to lessen the drug waiting time, as what has been mentioned above, enables the quick application of anti-seizure medicine for the patients and lessens the plausibility of Refractory SE.

Results

According to the review of the medical records and the information from the Integrated Epilepsy Research Group, it is revealed that among the number of patients underwent Electroencephalography (EEG) investigation, 35 were reported with SE. The average waiting time for diagnosis by the physicians is 154.77 minutes (1 to 53 hours) and the average time of medical receiving is 41.74 minutes (1 to 150 minutes). Based on the data from the pharmacy department of Srinagarind Hospital recorded in 2017, the average waiting time for receiving emergency medicine is 13.09 minutes, which is time starting from the raising of the doctor's prescription on the hospital online database to the medicine dispensing as illustrated in Table 1. The medical trafficking time to the patient's ward is excluded from this operation.

Table 1 shows that the waiting time to obtain emergency medicine ranks from 11.26 to 15.14 minutes (mean = 13.09 minutes). The waiting time involves many processes including the raising of the doctor prescription to the pharmacist's dispensing of the medicine. The time the nurses spend in searching for the medical administration methods and the trafficking of the medicine to the patient wards are excluded from this calculation. The application of SE Box can dramatically help nurses to have faster access to the medicine after gaining a doctor's approval. The superseding of time-consuming procedures in medical dispensing is a direct merit of SE box that can significantly reduce the time it takes for the SE patients to attain treatment. Since the SE Box has been introduced in November 2018, it was observed during the onset of SE Box application that a relatively small amount of medicines in the package was used. This resulted from the fact that the practitioners did not know thoroughly about the application of the SE Box. Information about the SE Box usage is presented in Table 2.

Table 1. Monthly averages of waiting times to obtain emergency medicines in 2017

Month	Average (minutes)
January	13.49
February	12.14
March	14.44
April	14.39
May	12.00
June	11.49
July	13.37
August	14.01
September	11.26
October	13.28
November	15.14
December	12.17
Total (Average)	13.09

Table 2. List of patients wards and records of the medicines used between December 2018 to July 2019

Month	Patient wards	Levetiracetam	Phenobarbital	Phenytoin	Sodium Valproate
December 2018	Intermediate care surgical ward 3B			/	
	Accident & Emergency 3				/
	Accident & Emergency 3			/	
	Neonatal Intensive Care Unit		/		
		/			
January 2019	Intermediate care surgical ward 3B				/
	Accident & Emergency 3			/	
	Surgical ward 3C			/	
	Male medicine ward 4A	/			
	Surgery Intensive Care Unit	/			
February 2019	Accident & Emergency 2			/	
	Accident & Emergency 3	/		/	
	Surgical ward 3B			/	
	Intermediate care surgical ward 3B			/	
	Accident & Emergency 2	/			
March 2019	Accident & Emergency 3	/		/	
	Surgery Intensive Care Unit			/	
	Accident & Emergency 2			/	
April 2019	Intermediate care medicine ward 4B	/			
	Intermediate care medicine ward 4B	/		/	
	Intermediate care medicine ward 4B		/		/
	Accident&Emergency2			/	
	Accident&Emergency3	/			
	Intermediate care medicine ward 4B				/
	Accident&Emergency2		/		
	Accident&Emergency2		/		
	Accident&Emergency2	/	/		
May 2019	Intermediate care medicine ward 4B	/			
	Surgical ward 3B			/	
June 2019	Intermediate care medicine ward 4B	/			
	Medicine Intensive Care Unit 2				/
	Intermediate care medicine ward 4B				/
	Intermediate care medicine ward 4B				/
	Cardiac Care Unit	/			
	Surgical ward 3B			/	
	Medicine Intensive Care Unit 2				/
July 2019	Medicine Intensive Care Unit 2		/		
	Cardiac Care Unit	/			
	Surgery Intensive Care Unit	/			
	Surgery Intensive Care Unit	/			
	Surgical ward 3B				/
	Surgical ward 3B			/	
	Intermediate care surgical ward 3B			/	
	Intermediate care medicine ward 4B	/			
	Medicine Intensive Care Unit 2		/		
	Medicine Intensive Care Unit 2		/		

As shown in Table 2, the medicine from the SE Box that is used the most in a ward is MICU2, followed by AE2. The first two medicines that are most often used are phenytoin and levetiracetam. It is also shown in Table 2 that more and more medicines from SE Box are used, which is the result of the broadcasting of the SE Box by the Integrated Seizure Research Group of Srinagarind Hospital Khon Kaen University is aware of the need to develop measures to help to subside the seizure among its patients. This is where SE Box can fit in to make the dispensing of the SE medicines more effective and reduce the threatening that seizure has on the patients' health.

Conclusion

The development of anti-seizure medical system in the patient wards of Srinagarind Hospital, Khon Kaen University, has resulted in the production of SE Box which is a medical dispensing innovation that is efficient in reducing

the amount of waiting time prior to applying medication to the patients. The SE Box is ready and convenient for use. Following a doctor's approval, the nurses on duty can apply the medicine to the patients by conveniently following the instructions available in SE Box. The instructions include loading dose, maintenance dose, medical feeding rate, preparing method, and cautions on application. The package reduces the error and the time to search for the medical instructions, while the SE Box can supersede the problem of storing medicines at the patient ward. The medicines stored at the patient wards can be expired after long storage. SE Box reduced errors on the medical application because the package has been monitored by pharmacists. However, it is important to emphasize on the accuracy of the medication dispensing. For this purpose, it is advised that the pharmacists conduct training to disseminate information on the use of SE Box to related practitioners. It is observed in this research that SE Box can increase the efficiency of the treatment for SE and acute seizure. It is also evidenced in this research that the SE Box has been used frequently after time while no questions relating to the application of the package have been raised, which can be interpreted that the SE Box is easy and effective for exploitation. There might be more promotion of the use of SE Box in the future; the evaluation of the users' satisfaction should be conducted in order to gain more insight into the improvement of SE Box.

What is already known on this topic?

SE is an urgent condition and must be treat immediately to decrease the chance of developing RSE. The key is to shorten the time of diagnosis and treatment. As we know, there were many process for patients to receive the medications including ordering process by doctors, preparing process by pharmacists, transferring process by logistic workers and administration process by nurses. Therefore, reducing those steps can be a way lead to succeed in SE treatment.

What this study adds?

The present study shows that the production of SE Box which is a medical dispensing innovation is efficient in reducing the amount of waiting time prior to applying medication to the patients. The SE Box is ready and convenient for use. SE Box can be a tool leads to development in status epilepsy and acute seizure treatment in the future.

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Potential conflicts of interest

The authors declare no conflicts of interest.

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การพัฒนาระบบยากันชักสำหรับภาวะชักต่อเนื่องและภาวะชักเฉียบพลัน

เพียงขวัญ นครรัตนชัย, นันทพรรณ์ ชัยนิรันดร์, สมศักดิ์ เทียมเก่า, สุณี เลิศสินอุดม, รัชฎาพร สุนทรภาส, ในนามของกลุ่มวิจัยโรคลมชักแบบบูรณาการ มหาวิทยาลัยขอนแก่น

ภูมิหลัง: ภาวะชักต่อเนื่อง (Status Epilepticus; SE) เป็นปัญหาอย่างหนึ่งในการดูแลผู้ป่วยเนื่องจากสามารถทำให้เกิดความพิการและอัตราการเสียชีวิตสูง การรักษาที่สำคัญคือการควบคุมการชักให้หยุดได้ภายใน 1 ชั่วโมง ข้อผิดพลาดที่พบบ่อยในการรักษา ได้แก่ การวินิจฉัยล่าช้า การให้ยาผิดขนาด ผิดวิธี ผิดอัตราเร็ว การผสมยาที่ไม่เหมาะสม

วัตถุประสงค์: ทีมสหสาขาวิชาชีพกลุ่มวิจัยโรคลมชักแบบบูรณาการได้ทำการพัฒนาระบบยากันชักในหอผู้ป่วยโดยจัดทำกล่องยากันชักพร้อมใช้ (SE Box) เพื่อลดระยะเวลาในการได้รับยา โดยใช้ในผู้ป่วย SE และ Acute Seizure

วัสดุและวิธีการ: SE Box ประกอบด้วยยากันชักชนิดฉีด 4 รายการ ได้แก่ phenytoin, phenobarbital, sodium valproate และ levetiracetam พร้อมเอกสารรายละเอียดของยากันชัก โดยกล่องจะถูกเตรียมโดยเภสัชกรหากมีผู้ป่วย SE หรือ acute seizure พยาบาลสามารถหยิบยาจากกล่องมาใช้ทันทีหลังคำสั่งใช้ยาของแพทย์

ผลการศึกษา: จากการทบทวนเวชระเบียน พบว่าค่าเฉลี่ยระยะเวลาในการวินิจฉัยเท่ากับ 154.77 นาที (1 ถึง 53 ชั่วโมง) และค่าเฉลี่ยในการได้รับยาเท่ากับ 41.74 นาที (1 ถึง 150 นาที) ระยะเวลารอคอยยาด่วนมีค่าเฉลี่ยเท่ากับ 13.09 นาที ซึ่งเป็นระยะเวลารอคอยที่นับตั้งแต่แพทย์เริ่มบันทึกคำสั่งการรักษาจนถึงการตรวจสอบยาโดยเภสัชกร SE Box สามารถลดระยะเวลารอคอยตรงนี้ให้เป็นศูนย์พยาบาลสามารถใช้ยาโดยอ้างอิงจากเอกสารที่อยู่ในกล่อง

สรุป: การพัฒนาระบบการให้ยากันชักในโรงพยาบาลศรีนครินทร์โดยใช้ SE Box เป็นนวัตกรรมทางการแพทย์อย่างหนึ่งสามารถลดระยะเวลารอคอยและเพิ่มความสะดวกในการให้ยาของผู้ป่วย