Anticonvulsant Drug Regimen and Cost of Acute Treatment for Status Epilepticus in a Philippine Tertiary Hospital: A Retrospective Cohort Study

Prima Kristina Paola V. Quintay, MD, Liz Edenberg P. Quiles, MD and Artemio A. Roxas Jr., MD

Institute of the Neurological Sciences, The Medical City, Pasig City, Philippines

ABSTRACT

Background. Status epilepticus (SE) is a neurological emergency requiring prompt evaluation and management to prevent disease refractoriness associated with significant mortality and morbidity. Thus, estimating costs attributable to the treatment of SE is important because of the severity of this disease. In the Philippines, healthcare provisions are mostly out-of-pocket expenses; hence the cost of treatment is a critical determinant for disease management. Unfortunately, the availability of data regarding the cost of illness of SE in developing countries is limited.

Objectives. To determine the frequently used anticonvulsant drug regimen and direct inpatient costs of acute treatment for status epilepticus within five years in a private tertiary hospital in the Philippines.

Methods. Records from patients diagnosed with SE who were admitted under or referred to the Adult Neurology Service in a private tertiary hospital from January 2015 to December 2019 were retrospectively evaluated. The SE type was classified as non-refractory (NRSE), refractory (RSE), and super refractory (SRSE). Demographic data, clinical features, SE type, etiology, antiepileptic drugs (AEDs) and anesthetic drugs used, total cost of AEDs and anesthetic drugs, total cost of 5-day hospitalization, and total cost of entire length of stay were recorded.

Results. We retrieved the records of 61 patients admitted for SE. Of these patients, 23 were classified as non-refractory, 20 as refractory, and 18 as super refractory. Diazepam was given to all SE patients as first-line treatment. Valproic acid and levetiracetam were used as second-line treatments. The most frequently given anesthetic drug was midazolam. The mean hospitalization cost per patient was ₱52,0982.3 for SE, ₱659,638.7 for RSE, and ₱134,1451 for SRSE. The mean cost of 5-day hospitalization was ₱193,572.3 for NRSE, ₱358,808.5 for RSE, and ₱652,781 for SRSE. The mean cost of medications was ₱18,546 for NRSE, ₱30,780 for RSE, and ₱128,263 for SRSE.

Conclusion. The direct cost of SE varied depending on subtype and response to treatment. Costs increased with disease refractoriness. Direct inpatient treatment costs for SRSE were twice as high as that of NRSE and RSE.

Keywords: inpatient treatment cost, anticonvulsant drug regimen, epilepsy, status epilepticus, hospitalization

eISSN 2094-9278 (Online)
Published: June 28, 2023
https://doi.org/10.47895/amp.vi0.4921

Corresponding author: Prima Kristina Paola V. Quintay, MD
Institute of the Neurological Sciences, The Medical City
Ortigas Avenue, Pasig City 1600, Philippines
Email: pvquintay@themedicalcity.com
ORCiD: https://orcid.org/0000-0001-5220-9891

INTRODUCTION

Background

Status epilepticus (SE) is a neurological emergency that entails prompt evaluation and management to prevent disease refractoriness associated with significant mortality and morbidity. It is imperative to control overt and electrographic seizures as the risk of cerebral damage increases progressively after 1-2 hours of continuous status.[1] Treatment for patients with SE is resource-intensive as it uses multiple drugs and requires close monitoring. Therefore, estimating costs

attributable to the treatment of SE is important because of the severity and cost of this disease.

Increasing disease refractoriness is associated with higher hospitalization costs and worse clinical outcomes. Studies have demonstrated that SE has a high economic burden on the health care system, patients, and their families.[2] With growing resource utilization and limitations of accessible healthcare resources, it is essential to provide cost estimates to plan resource allocation and health policy decision-making.[3] In the Philippines, healthcare expenses are mostly paid out-of-pocket; hence, cost of treatment is a critical determinant for compliance in disease management. Available data is limited regarding the cost of illness of SE in developing countries. This study aims to report frequently used anticonvulsant drug regimens and hospitalization costs for status epilepticus over 5 years in a single-center Philippine tertiary hospital. This study may also provide socioeconomic impact by evaluating the cost of SE.

Table 1. Cerebral Performance Category (CPC)[5]

Score	Definition
1	***Good cerebral performance.*** Conscious, alert, able to work and lead a normal life, may have minor deficits.
2	***Moderate cerebral disability.*** Conscious, sufficient cerebral function for part-time work in sheltered environment or independent activities of daily life (dress, travel by public transportation, food preparation).
3	***Severe cerebral disability.*** Conscious, dependent on others for daily support (in an institution or at home with exceptional family effort). Has at least limited cognition. This category includes a wide range of cerebral abnormalities, from patients who are ambulatory but have severe memory disturbances or dementia precluding independent existence, to those who are paralyzed and can communicate only with their eyes, as in the "locked-in" syndrome.
4	***Unconscious.*** Unaware of surroundings, no cognition No verbal and/or psychologic interaction with environment.
5	***Dead.*** Brain dead, or dead by conventional criteria.

METHODS

This is a descriptive retrospective cohort study of all adult (aged 18 years old and above) patients diagnosed to have SE admitted under or referred to the Adult Neurology Service from January 2015 to December 2019. All patients were admitted for at least five days. Patients were further classified into the following: Non-refractory Status Epilepticus (NRSE), defined as seizures lasting for 5 minutes or longer, or no regain of consciousness for approximately 5 minutes from seizure onset, not fulfilling the definition for RSE and SRSE; Refractory status epilepticus (RSE) defined as generalized convulsive seizure unresponsive to treatment with 2 AEDS or requiring anesthetic agent; Super refractory status epilepticus (SRSE) defined as seizures that continues for 24 hours or more after the onset of anesthesia or those that recur on the reduction or withdrawal of anesthesia.[4]

Patients diagnosed with status epilepticus were identified using the Department of Neurology daily inpatient census. We manually screened and collected data using digital and printed medical records. Chart review was done for each patient identified. Direct cost data were provided by the hospital billing computer system.

The main categories were the subtypes of SE (NRSE, RSE, SRSE). Patient demographics (age, gender) were identified. Clinical parameters were also classified based on etiology (structural, infectious, metabolic, immune, unknown), outcomes (Table 1. Cerebral Performance Category), length of ICU stay, and length of hospitalization. Frequently used antiepileptic drugs (AEDs) and anesthetic drugs used in the management of SE were also identified.

Total direct cost during the entire hospitalization was determined in this study by calculating the 1) total inpatient cost of 5-day hospitalization and 2) total cost of AEDs and anesthetic drugs given until the patient was deemed seizure-free for at least 24 hours. Results were reported according to subtype. Descriptive statistics were used for frequency and percentages of the identified treatment medications, costs, and cost parameters.

Cost

A standard cost for each medication was used based on its price in the hospital. Cost of medications (AED and anesthetic drugs) was computed as the total amount of AEDs (and anesthetic drugs, if given), both IV and oral, on all days that the patient has active seizures and an additional day that the patient was seizure-free. Direct inpatient cumulative costs for a 5-day hospitalization and the entire length of stay were also obtained in this study through the electronic charging system used in the hospital. Total direct hospitalization costs were calculated for 5 different years, with the inflation rate in 2019 as the basis. The total hospitalization costs in the preceding years were then multiplied by the inflation rate as provided by the Central Bank of the Philippines statistics.[6] Professional fees were excluded from the computation since it varied among physicians. The costs were calculated in Philippine Peso (₱).

RESULTS

We retrieved the records of 61 patients admitted for SE. We classified 23 patients as NRSE, 20 as RSE, and 18 as SRSE. Table 2 summarizes the demographic features, clinical characteristics, and outcomes of patients with SE. Most patients with NRSE had structural etiology (52%), whereas both RSE and SRSE were mostly metabolic (55% and 83%, respectively). The mean age for all subtypes was in the 50s. Patients were mostly women (61%) for NRSE, equal for RSE, and predominantly men (61%) for SRSE. Majority of NRSE patients (43%) had a significant disability upon discharge, while most RSE and SRSE patients resulted in death. The length of hospitalization and length of ICU

stay were included as cost determinants in this study. The mean ICU stay was longest for SRSE (12.8 days), followed by 10.8 days for RSE, and 6 days for NRSE. The mean hospitalization stay was longest for RSE (20.9 days), followed by 19.9 days for SRSE, and 18 days for NRSE.

The primary treatment in SE patients is summarized in Table 3. The initial treatment given in all SE patients was benzodiazepine, specifically diazepam. In NRSE patients, the most frequently used 2nd line AEDs was levetiracetam (65%) followed by valproic acid (43%), both in 1–2 g doses. In RSE patients, the most frequently used AED was valproic acid 500mg IV dose (35%) followed by 1–2 g dose of VPA given to 30% of patients. The patients with SRSE most frequently received levetiracetam 1–2g doses (61%), followed by valproic acid 1–2g dose (56%). The most commonly used anesthetic drug was midazolam, given in 90% of patients with RSE and 83% with SRSE. As for maintenance medication, 52 % of patients with NRSE and 60% of those with RSE were on monotherapy of AED (levetiracetam or valproic acid), whereas 56% of patients with SRSE were mostly on three or more AEDs (levetiracetam, valproic acid, clonazepam).

Table 4 presents the cost of SE treatment. The mean 5-day hospitalization cost was highest for SRSE (₱652781), followed by RSE (₱358808.5) and SE (₱193572.3). Similarly, the mean AED cost was highest for SRSE ₱67,532), followed by RSE (₱20,598) and NRSE (₱18,546). The mean anesthetic drug cost was higher for SRSE ₱56,140.2) than for RSE (₱10,182.5). The mean total cost of AEDs and anesthetics was also higher for SRSE (₱128,263) than for RSE ((₱30,780). Mean hospitalization cost was highest for SRSE (₱1,341,451.0), followed by ₱659,638.7 for RSE and ₱520982.3 for SE. Overall, an increasing trend was noted regarding costs as SE becomes more severe or refractory.

DISCUSSION

The impact of SE is substantial both because of the high cost and the number of cases, particularly in the middle-

Table 2. Demographic and clinical characteristics, and outcomes of SE admissions

		NRSE (n = 23), n (%)	RSE (n = 20), n (%)	SRSE (n = 18), n (%)
Etiology	Structural	12 (52)	8 (40)	1 (5)
	Infectious	2 (9)	1 (5)	0
	Metabolic	9 (39)	11 (55)	15 (83)
	Immune	0	0	2 (11)
	Unknown	0	0	0
Sex	Male	9 (39)	10 (50)	11 (61)
	Female	15 (61)	10 (50)	7 (39)
Age	Mean ± SD	55.1 ± 16.7	54.20 ± 18.2	50 ± 20.7
Outcome (CPC)	1-2	8 (35)	5 (25)	2 (11)
	3-4	10 (43)	7 (35)	3 (17)
	5	5 (22)	8 (40)	13 (72)
Length of ICU stay	Mean ± SD	6 ± 8.5	10.8 ± 9.1	12.8 ± 7.5
Length of hospitalization	Mean ± SD	18 ± 8.7	20.9 ± 14.38	19.9 ± 15.51

Table 3. Use of AEDs and anesthetics on initial management of SE

	NRSE (n = 23), n (%)	RSE (n = 20), n (%)	SRSE (n = 18), n (%)
First-line therapy			
Diazepam IV	23 (100)	20 (100)	18 (100)
Second-line therapy			
Levetiracetam IV (1g–2g)	15 (65)	5 (25)	10 (56)
Levetiracetam IV (500 mg)	5 (21)	2 (10)	2 (11)
Valproic acid IV (1g–2g)	10 (43)	6 (30)	11 (61)
Valproic acid IV (500 mg)	1 (4)	7 (35)	1 (5)
Third-line therapy			
Propofol	0	2 (10)	6 (33)
Midazolam	0	18 (90)	15 (83)
Number of AEDs maintained			
1 AED	12 (52)	12 (60)	1 (5)
2 AEDs	9 (39)	7 (35)	7 (39)
3 or more AEDs	2 (8)	1 (5)	10 (56)

AEDs, antiepileptic drugs; SE, Status epilepticus; IV, Intravenous

Table 4. Direct cost of treatment for status epilepticus (₱)

	NRSE (Mean ± SD)	RSE (Mean ± SD)	SRSE (Mean ± SD)
5-day hospitalization cost	193,572.3 ± 119,431.32	358,808.5 ± 117,089.8	652,781 ± 245,138.9
Cost of AEDs *(until seizure-free for at least 24 hours)*	18,546 ± 11,498	20,598.3 ± 12,171.2	67,532 ± 47,527
Cost of Anesthetic drugs *(until seizure-free for at least 24 hours)*	-	10,182.5 ± 8,117.3	56,140.2 ± 99,159.4
Total cost of AEDs + Anesthetic drugs *(until seizure-free for at least 24 hours)*	18,546 ± 11,498	30,780 ± 16,585	128,263 ± 143,629
Total hospitalization cost	520,982.3 ± 441,011.5	659,638.7 ± 244,460.0	1,341,451 ± 939,221.9

AEDs, antiepileptic drugs; SE, Status epilepticus

aged and elderly. In this paper, we investigated frequently used anticonvulsant drug regimens and the cost of acute treatment for SE in a Philippine tertiary hospital. We found that diazepam was given in all patients with SE. In a 2020 study in Japan, diazepam was also the most frequent first-line management for SE from 2011–2017.[7] More recent work has shown that midazolam or lorazepam may serve as alternative drugs and have some advantages over diazepam; however, the more established action of diazepam makes it the primary choice for the initial management of SE.[1] Some studies, however, show that lorazepam is the first-line benzodiazepine of choice once there is IV access due to its more predictable effect from a smaller volume of distribution and its lack of active metabolites as compared to diazepam.[8] Lorazepam is not available in the Philippines.

The emergence of newer AEDs, such as levetiracetam and fosphenytoin, shifted the second-line therapy for SE from phenytoin and phenobarbital. Beginning in 2015, both IV and oral levetiracetam use increased rapidly and were predominantly prescribed in preference to other AEDs in Japan.[7] Most patients in our report were given IV levetiracetam and valproic acid for acute SE treatment. Fosphenytoin, currently priced at around ₱50,000 per vial, was not utilized among our patients. Levetiracetam has been more frequently used and has a favorable side-effect profile than valproic acid, phenytoin, and fosphenytoin. Valproic acid, being an older drug, is well-established in the treatment algorithm of SE. Some studies showed that valproic acid was superior in aborting SE than fosphenytoin and phenytoin.[8] For third-line treatment for patients with RSE and SRSE, Neurocritical Care guidelines recommend midazolam (Level IIb A) over propofol (Level IIb B).[8] In our study, midazolam was mostly used as a third-line treatment, followed by propofol.

Studies on the economic burden of SE have focused primarily on the direct costs of treatment and have been conducted in high-income country settings. SE-related costs in 2018 were estimated at $14,500 (₱759,800) in the United States.[9] SRSE costs were twice as high as NRSE and RSE costs. It was also shown that mortality was much higher in SRSE. Similarly, in this paper, NRSE and RSE mean hospitalization costs were at ₱520,982 and ₱659,638, respectively, whereas SRSE costs were also estimated to be twice as much. In a 2012 healthcare utilization report of patients with epilepsy in Germany, SE-related mean admission costs were €8,347 (₱605,574). Of these SE admissions, SRSE cost (€32,706: ₱2,372,493) was much higher than NRSE (€4063: ₱294,576) and RSE (€4581: ₱332,305).[10] In general, SRSE costs are still significantly higher among the types of SE across the studies cited. SRSE costs both in the US and Germany were estimated at $40,000-$50,000 (₱1,880,000–₱2,350,000).[11,12] A 2019 study in Turkey showed that the mean cost of treatment per patient was ₺22,202.86 (₱133,338.9), and the mean drug cost was ₺4,630 (₱27,805.4).[13] A more recent SE cost analysis in Turkey reported the average cost of medicine at ₺1,344.25 (₱8,072.9) and a total treatment cost of ₺4,197.02 (₱25,205.1).[14] Reports between these studies vary in a hospital setting where the 2019 study accounted for the entire hospitalization while the latter focused on ICU charges only. In the acute setting, medication costs in our study were much higher. The disparity may be due to healthcare expenditures in Turkey being largely funded by the public sector.[15]

A study by Penberthy in 2005 found that the average length of hospital stay was 12.9 days.[2] In another study by Strzelczyk in 2013, the mean hospitalization was 14 days.[3] The specific SE classification was not stated in both papers, but our current study gathered an overall longer hospital stay for SE patients. Compared to the previously cited studies where hospital costs are largely covered by health insurance, out-of-pocket expenses remain to be the major source of financing for medical care in the Philippines. Some patients stay longer in the hospital because they are unable to pay hospital bills.

In the same way, additional costs accumulate due to prolonged stay. PhilHealth, a public sector insurance, provided a list of medical case rate coverages in 2017, where SE was categorized under epilepsy. A case rate was subsidized at ₱7,800, and healthcare institution fee at ₱5,460. Given the data provided in this current study, only less than 10% of total hospitalization cost was covered by PhilHealth.

Limited literature is available on evaluating the cost of SE in a developing country. A 2017 study in India determined total hospital expenses, and the results had a mean

of INR19,900 (₱15,408).[16] However, RSE and SRSE were not included. Hospitalization costs obtained in our current study were much higher. Although both were done in developing countries, differences may have been due to the inclusion of government hospitals in their study. In contrast, ours was only in a single private tertiary hospital. Medications are also generally less expensive in India.

In this study, the practice of maintaining patients with active seizures on IV AEDs has a huge difference in costs as 1 gram of IV levetiracetam was at ₱4,747 and 1gram of IV valproic acid was at ₱3,053, compared to the oral solution of the same dose, for levetiracetam at ₱101 and valproic acid at ₱151. As per the definition of SRSE as seizures continuous for 24 hours or more, being on IV antiepileptic medications cumulative for every day that the patient has seizures, the total treatment costs and, therefore, hospitalization costs for SRSE are much higher. More prolonged ICU admissions, monitoring equipment, and management for other multiple comorbid conditions associated with SRSE may have been attributed to its significantly higher inpatient costs. Also, most patients with refractory SE were post-arrest. All of them underwent therapeutic hypothermia, most were on vasopressors, some had cardiac procedures, and some underwent hemoperfusion; all of which utilized items that added up to the total inpatient treatment cost. Post-arrest seizures have been associated with poor outcome, with 83.3% resulting in demise, as also seen in our study where most post-arrest patients died.[17]

Healthcare systems among countries greatly vary. Some countries largely depend on health insurance, whereas others, like the Philippines, are mostly out-of-pocket expenses. Disparities in total treatment costs in this study have also been noted due to the extended hospitalization of some patients because of their inability to pay hospital bills.

CONCLUSION

Frequently used anticonvulsant drugs observed in this study for acute treatment of SE starts with diazepam as first-line, valproic acid or levetiracetam IV as second-line, and midazolam as third-line therapy. The mean cost of acute treatment was highest for SRSE (5-day hospitalization and mean cost of medications). The direct cost of SE varied depending on subtype and response to treatment. In general, costs increased with disease refractoriness and longer ICU stay. The direct inpatient treatment costs for SRSE were twice as high than that of NRSE and RSE.

Limitations

Professional fees were excluded in the costing data due to variations that may depend on each attending physician's years of practice, expertise, and preference. Indirect costs were not also included in this study. Comparison of results across previously reported data was difficult because of the differences in level and methods of data collection and economic values. Other limitations encountered were the small population and the single-center acquisition of data.

Recommendation

The authors would like to recommend a cross-sectional survey of all neurologists nationwide regarding their practice pattern in the management of SE. The data will provide an insight into how resource availability in different areas in the Philippines affects the management of patients with SE. Multicenter studies with a higher number of participants are also needed for a more comprehensive and accurate understanding of the cost of SE in the Philippines.

In this study, the authors propose to identify possible means of lowering hospitalization costs, such as providing treatment packages, and increasing financial subsidy, especially from the government, through appropriate resource allocation via health financing policies.

Statement of Authorship

All authors contributed in the conceptualization of work, acquisition and analysis of data, drafting and revising and approved the final version submitted.

Author Disclosure

All authors declared no conflicts of interest.

Funding Source

This study has no funding support.

REFERENCES

1. Shorvon S. The management of status epilepticus. J Neurol Neurosurg Psychiatry. 2001 Jun; 70: 22-7.
2. Penberthy LT, Towne A, Garnett LK, Perlin JB, DeLorenzo RJ. Estimating the economic burden of status epilepticus to the health care system. Seizure. 2005 Jan; 14(1):46-51.
3. Strzelczyk A, Knake S, Oertel WH, Rosenow F, Hamer HM. Inpatient treatment costs of status epilepticus in adults in Germany. Seizure. 2013 Dec; 22(10):882-5.
4. Trinka E, Kälviäinen R. 25 years of advances in the definition, classification, and treatment of status epilepticus. Seizure. 2017 Jan; 44:65-73.
5. Reynolds EC, Soar J. How are cerebral performance category scores measured for audit and research purposes? Resuscitation. 2014 May; 85(5):e73–e74. doi.org/10.1016/j.resuscitation.2014.01.011
6. Bangko Sentral ng Pilipinas, Inflation rates [Internet]. 2021 [cited 26 August 2021]. Available from: https://www.bsp.gov.ph/statistics/spei_pub/Table%2034.pdf
7. Nakamura K, Ohbe H, Matsui H, Takahashi Y, Marushima A, Inoue Y et al. Changes in Real-world Practice Patterns of Antiepileptic Drugs for Status Epilepticus: A Nationwide Observational Study in Japan. Neurol Med Chir. 2020 Mar; 60(3):156-63.
8. Billington M, Kandalaft OR, & Aisiku IP. Adult Status Epilepticus: A review of the prehospital and emergency department management. J Clin Med. 2016 Aug; 5(9).
9. Fernández IS, Loddenkemper T. Estimating the cost of admissions related to convulsive status epilepticus in the United States of America. Seizure. 2018 Oct; 61:186-98.
10. Strzelczyk A, Nickolay T, Bauer S, Haag A, Knake S, Oertel WH, et al. Evaluation of healthcare utilization among adult patients with epilepsy in Germany. Epilepsy Behav. 2012 Apr; 23(4):451-7.

11. Kortland LM, Knake S, Rosenow F, Strzelczyk A. Cost of status epilepticus: A systematic review. Seizure. 2015 Jan; 24:17-20.
12. Beg JM, Anderson TD, Francis K, Meckley LM, Fitzhenry D, Foster T, Sukhtankar S, Kanes SJ, Moura LMV. Burden of illness for super-refractory status epilepticus patients. J Med Econ. 2017 Jan; 20:45-53. doi: 10.1080/13696998.2016.1223680
13. Keskin Guler S. Cost of inpatient treatment of patients with status epilepticus in Turkey. Epilepsi. 2019 Jan; 27(3).
14. Celik H, Yardim A. Cost analysis on status epilepticus patients treated in intensive care units. Med Science. 2020 Sep; 9(3):731.
15. Atun R. Transforming Turkey's health system — lessons for universal coverage. N Engl J Med. 2015 Sep; 373(14):1285-9.
16. Misra UK, Kalita J, Bhoi SK, Dubey D. Cost of status epilepticus in a tertiary care hospital in India. Seizure. 2015 Sep; 31:94-98.
17. Quiles LE, Fernandez ML. Prognosis following seizures after successful cardiopulmonary resuscitation: a retrospective cohort study. Phil J Neurol. 2021 Jul; 24(1).