Seizure 31 (2015) 94–98

Contents lists available at ScienceDirect

Seizure

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

Cost of status epilepticus in a tertiary care hospital in India

Usha K Misra *, Jayantee Kalita, Sanjeev K. Bhoi, Deepanshu Dubey

Department of Neurology Sanjay Gandhi Post Graduate Institute of Medical Sciences, Lucknow, India

ARTICLE INFO

Article history:
Received 17 April 2015
Received in revised form 13 July 2015
Accepted 15 July 2015

Keywords:
Status epilepticus
Cost
India
Predictors
Mortality
Disability

ABSTRACT

Purpose: Status epilepticus (SE) is one of the most important neurological emergencies. The present study evaluated both direct cost of SE and predictors of cost in an Indian tertiary care teaching hospital in Lucknow India.

Methods: SE was defined as continuous seizure for ≥5 min or recurrent seizures without regaining consciousness. Etiologies of SE were categorized as acute central nervous system (CNS) pathology, acute non-CNS pathology, chronic CNS pathology, congenital disorders and others. Patients requiring mechanical ventilation (MV) received ventilators free of cost. Mortality and disability on discharge were noted.

Results: Fifty-five patients aged 8–90 years were included (males, 33). Fifty (89.3%) patients had generalized convulsive SE. The severity of SE as assessed by Status Epilepticus Scoring Scale was unfavorable (score, 3–6) in 41 (74.5%) patients. The etiology of SE was categorized as acute CNS pathology in 28 (51%) patients, non-CNS and chronic CNS pathology in 11 (19.6%) patients each, remote congenital pathology in 2 (3.6%), and others in 3 (5.6%). Thirty (53.6%) patients had comorbidities. Median duration of hospitalization was 7 (range, 1–72) days.Twenty six patients were hospitalized for >7 days. SE was controlled by 2 drugs in 47 (85.5%) patients and refractory to 2 intravenous antiepileptic drugs in 8 (14.5%). Nineteen (34.5%) patients died, and 29 (51.8%) showed favorable outcomes on discharge. Median hospital expenditure per case was INR 19,900 ($309.87; range, INR 1600–574,000). On multivariate analysis, SE hospitalization costs were determined by refractoriness of SE and mechanical ventilation (MV). Hospitalization cost of SE was lower than those of stroke.

Conclusion: Acute non-CNS pathology is largely responsible for the high cost of SE, particularly refractory SE requiring mechanical ventilation.

1. Introduction

Status epilepticus (SE) is a well-known neurological emergency and one of the most common reasons for admission to a neurological emergency department, second only to stroke. The prevalence of SE in the US has been estimated as 18.3–41.0 per 100,000 population [1,2]. Considering the greater prevalence of central nervous system (CNS) infections and infestations in developing countries, the incidence of SE is likely to be higher in such countries than in developed countries [3]. In addition, infections and infestations are the most common etiologies of SE in developing countries compared with developed countries, where stroke and drug withdrawal are the most common etiologies [3,4]. There are regional differences in the treatment protocol as well. In developed countries, SE is managed in the intensive care unit (ICU), whereas in developing countries, it is managed in general ward due to paucity of ICU.

The cost of SE is determined by multiple factors such as drugs, invasive and noninvasive monitoring, investigations, supporting infrastructure, and specialized manpower. There have been few studies especially from developing countries calculating the cause of SE. A US study estimated an annual direct cost of $4 billion for SE and found that the direct inpatient cost was higher than the direct cost of acute myocardial infarction or congestive heart failure [5]. According to another study from Germany, acute treatment of SE was responsible for the high proportion of hospital costs associated with epilepsy. Healthcare systems are likely to encounter a higher incidence of SE and its associated costs owing to the high incidence of SE in the elderly population, thus emphasizing the need to further assess the burden and optimize the treatment of SE [6]. A systematic review confirmed SE as a cost-intensive disorder and emphasized the urgent need for detailed and comprehensive cost of illness studies [7]. However, no such

* Corresponding author. Tel.: +91 522 2494167; fax: +91 0522 2668017.
E-mail addresses: drukmisra@rediffmail.com, drukmisra@gmail.com (U.K. Misra).

http://dx.doi.org/10.1016/j.seizure.2015.07.009
1059-1311/

studies have been conducted in developing countries, where cost of treatment is a critical determinant of disease management. In this review, we report the direct cost of SE during hospitalization as well as the predictors of cost.

2. Subjects and methods

SE patients admitted during September 2013 to January 2015 were retrospectively analyzed.

2.1. Inclusion criteria

- Patients with SE, defined as continuous convulsions for ≥5 min or recurrent seizures without recovery of consciousness to baseline between the attacks
- Patients with subtle SE, defined as the presence of coma and ictal discharges on electroencephalogram (EEG), along with subtle convulsive movements [8]
- Patients whose expenditure during hospitalization could be retrieved from the computerized hospital information system

2.2. Exclusion criteria

- Patients whose expenditure during hospitalization could not be retrieved from the computerized hospital information system

3. Management

Patients were initially treated with lorazepam (LOR), which was repeated if the seizures were not controlled within 2 min of the first dose. Second-line antiepileptic drugs such as phenytoin (PHT), sodium valproate (SVA), or levetiracetam (LEV) were prescribed if the SE continued after the second dose of LOR. Patients were managed in the ICU until their condition was stabilized and the underlying cause of seizures was managed. Outcome was defined as cessation of seizures for 24 h, death, or discharge from the hospital.

Etiologies of SE were categorized into the following groups: [5]

- Acute CNS pathology such as stroke, encephalitis, and meningitis
- Acute non-CNS pathology such as pneumonia, renal failure, liver failure, metabolic disturbances, and malignancies
- Chronic CNS pathology such as calcific granuloma, old stroke, and old head injury
- Congenital pathology
- Others (hypoxia after cardiopulmonary resuscitation, old CNS causes precipitated by recent illness, and alcohol withdrawal)

The severity of Status Epilepticus was defined by status epilepticus Severity Score (STESS) which was calculated using the level of consciousness (0, alert; 1, stupor or coma), seizure type (1, generalized; 2,nonconvulsive in coma; 0, others), age (0, <65 years; 1,≥65years), and history of previous seizures (0, present; 1, absent or unknown). Scores ranged from 0 to 6: 0–2 was considered favorable and 3–6 was considered unfavorable [9].

Direct cost was calculated by retrieving the cost incurred during hospitalization. The informal out-of-pocket expenses, including cost of transportation, supervision, cost incurred in the referring hospital and wages lost by caregivers or patients, were not included in this study. The modified Rankin's scale (mRS) was used to assess disability at discharge: a score of 0–2 indicated favorable outcome [10].

Fifty-five age-matched patients with stroke, (36 ischemic, 14 hemorrhagic, and 5 venous strokes) without SE admitted during the same period were randomly selected and their direct cost, morbidity and mortality were recorded and compared with those of patients with SE.

For comparison with international cost, we used the exchange rates on May 12, 2015:$1 = Indian Rupees (INR) 64.22 and €1 = INR 72.11.

4. Statistical analysis

The etiology of SE was compared with demographic, clinical, STESS, and direct cost of SE by using the parametric test for categorical and analysis of variance (ANOVA) for continuous variables. The cost predictors of SE management were evaluated using univariate regression analysis, followed by multivariate regression analysis, including the variables with a two-tailed p value of <0.1. Moreover, the outcome and cost of SE in different age groups were evaluated using the chi-square test for categorical and ANOVA for continuous variables. A two-tailed p value of <0.05 was considered significant. Statistical analysis was performed using Statistical Package for the Social Sciences (SPSS; version 16) software. GraphPad prism 5 was used for graphical presentation.

5. Results

Of the 56 patients with SE, 1 was excluded due to incomplete data. The median age of the patients was 40 (range, 8–90) years, and 33 (58.9%) patients were males. A majority of patients (50 [89.3%]) had generalized tonic clonic seizures. One (1.8%) patient had epilepsia partialis continua, and 4 (7.1%) had nonconvulsive SE. The STESS score was unfavorable in 41 (74.5%) patients.

The etiology of SE was acute CNS pathology in 28 (50%) patients: acute stroke in 9, encephalitis in 14, meningitis in 4, and inflammatory granuloma in 1 patient. In addition, the etiology was acute non-CNS pathology in 11 (19.6%) patients: acute renal failure in 3, chronic renal failure in 3, hyponatremia in 2, liver failure in 1, and sepsis in 2 patients. Moreover, the etiology was chronic CNS pathology in 11 (19.6%), remote congenital pathology in 2 (3.6%), and others in 3 (5.4%) patients. The median duration of SE before treatment initiation was 1 h (range, 0.08–240 min). Comorbidities such as diabetes, hypertension, uremia, liver disease, and malignancy were present in 30 (53.6%) patients, and 12 (21.4%) patients had more than one comorbidities. Twenty-seven (48.2%) patients required mechanical ventilation (MV). The median duration of hospitalization was 7 (range 1–72) days, and 26 patients required >7 days of hospitalization. SE was controlled within 1 h in 47 (85.5%) patients, and 8 (14.5%) patients had refractory SE (resistant to two intravenous antiepileptic drugs). Thirty-six (65.5%) patients were discharged from the hospital, of whom, 29 (51.8%) had favorable outcomes (Table 1); the median mRS score was 3. Nineteen (34.5%) patients died; the cause of death in all patients was not directly related to SE but due to underlying conditions.

The direct cost of SE ranged between INR 1600 and 574,000 (median, INR 19,900, US $309.87, or €275.96; Fig. 1). Univariate analysis revealed an association between death and hospitalization for <7 days ($p = 0.024$), STESS score ($p = 0.012$), comorbidities ($p = 0.008$), multiple comorbidities ($p = 0.07$), and MV ($p = 0.00$). The predictors of direct SE cost >INR 20,000 were hospitalization for > 7 days ($p = 0.01$), duration of SE >1 h ($p = 0.04$), and MV ($p = 0.01$) (Table 2). Patients aged 18–60 years incurred the lowest costs ($p = 0.05$, Table 3). On multivariate analysis, MV ($p = 0.002$) and hospitalization for <7 days were determined as predictors of death. In addition, disability was related to MV, and these patients incurred higher costs ($p = 0.001$).

Direct cost of the 55 age-matched stroke patients during the study period ranged between INR 3028 and 181,539(median: INR

Table 1
The demographic and clinical details of the patients with status epilepticus in different etiological groups.

		Acute CNS $N=27$	Chronic CNS $N=11$	Acute non CNS $N=11$	Remote congenital $N=2$	Others $N=3$
Female	10	6	4	1	0	
Age	<18yrs	3	2	2	1	1
	18–60yrs	18	7	7	1	2
	>60yrs	6	2	2	0	0
SE	Generalised	23	11	11	2	3
	Focal	1	0	0	0	0
	NCSE	3	0	0	0	0
Cost (median)INR	27271	8155	84089	16267	82532	
Disability (mRS < 3)	15	8	3	1	2	
STESS score <3	5	5	0	2	2	
Mechanical Ventilation	16	0	9	0	2/1	
Comorbidities Yes/no	12/15	6/5	10	0/2	½	
Stay in hospital days (median)	8	6	7	9.5	7	
Death	10	0	8	0	1	

CNS = central nervous system, INR = Indian rupees, NCSE = Non convulsive status epilepticus; SE = Status Epilepticus, STESS = Status Epilepticus Severity Score.

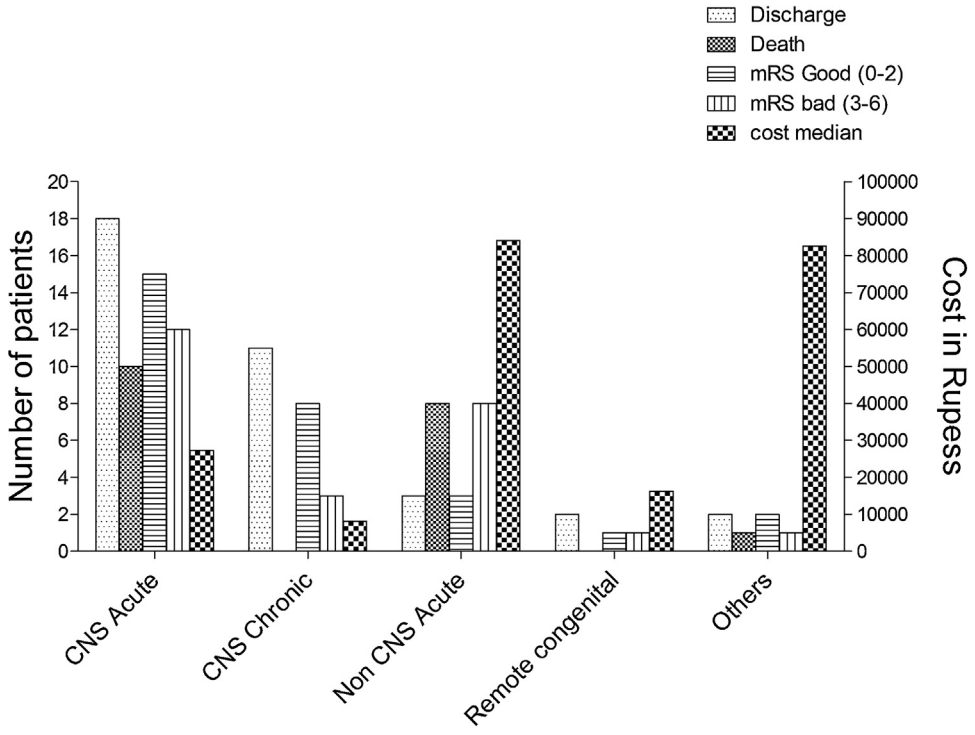

Fig. 1. Bar diagram shows the direct cost during hospitalization of status epilepticus (SE) due to different etiologies of SE.
CNS: central nervous system, mRS: modified Rankin scale.

14,932, $232.51,or €207.1), which was lower than that of SE patients. Four of these stroke patients died.

6. Discussion

The direct cost of SE, as determined by hospital expenses, was INR 19,900 ($309.87, €275.96). The highest costs were incurred by SE patients with acute non-CNS pathology, followed by those with acute CNS pathology, remote congenital CNS pathology, and the lowest in patients with chronic CNS pathology. The predictors of cost were hospitalization for >7 days, extremes of age, duration of SE >1 h, and MV. Multivariate analysis showed that only extremes of age and MV were independently related to direct cost of SE. The direct cost of SE management was higher than that of acute stroke but without statistically significant differences.

Table 2
Predictors of direct cost of status epilepticus treatment.

Patient group	<Rs 20000	>Rs 20000	P
Age 18–60 years	22	13	0.05
Hospitalisation > 7 days	8	17	0.01
Mechanical ventilation	9	18	0.01
Duration of SE	≤ 1 h	> 1 h	0.04

SE = status epilepticus.

To our knowledge, this is the first study that evaluated the direct cost of SE in a developing country. Our results are in agreement with those of another study, wherein elderly patients had higher mortality [11]. In our study, pediatric (age < 18 years) and elderly (age > 65 years) patients incurred higher costs than adults did. Moreover, the incidence of comorbidities, mortality, and morbidity was higher in elderly patients than in patients from other age groups.

In this study, the median hospital cost of SE (INR 19,900, $309.87, or€275.96) was much lower compared with that reported in the US ($8417) [5] or Germany (€1347) [6]. Overall

Table 3
Influence of age on the outcome and cost of status epilepticus patients.

Parameters	≤18 yrs $N=9$	18–60 yrs $N=36$	>60 yrs $N=10$	P value (≤18 vs. 18-60)	P value (≤18 vs. >60)	P value (18–60 vs. >60)
Death	2 (22.2%)	11(30.6%)	6(60.0%)	1.0	0.4	0.33
Comorbidity	1 (11.1%)	20 (56.6%)	9 (9.0%)	0.15	0.10	0.53
Multiple comorbidity > 2	1 (11.1%)	6 (16.6%)	5 (50.0%)	1.0	0.34	0.14
Ventilator	2 (22.2%)	17(47.2%)	8(80.0%)	0.48	0.23	0.51
Hospital stay > 7 days	2 (22.2%)	18 (50.0%)	6 (60.0%)	0.48	0.40	0.99
Cost (mean ± SD) in INR	82617.56 ± 98325.08	55973.91 ± 114711.48	92735.40 ± 119295.25	<0.05	<0.05	NS

NS = Non significant, INR = Indian rupees.

cost of 992 patients in a private ICU in India was INR 100,779,209 ($1569561.02 or €1397576.05). Cost per unit per day was INR 1973($32 or €27.36) [12]. Intensive care in India is much cheaper than in the West due to lower cost of drugs, wages, and use of consumables after resterilization, which is a common practice in Indian hospitals [12]. Reimbursement cost of SE in the US was $8417 [5].

Comparison with other neurological disorders may help in obtaining a relative estimate of the direct expenditure of SE. In our study, the direct cost of SE management was less than that for acute stroke. In a previous study, the cost per patient for SE was 60%–90% higher than that for stroke [5]. In our study, the cost of stroke treatment was not significantly different from SE. It is possible that because of the tertiary care referral nature of our facility, patients reached the hospital after the window period for recombinant tissue plasminogen activator (rtPA) treatment was over. Moreover, lack of rtPA therapy may be responsible for the lower cost of stroke treatment. A study from Germany screened 96 patients with epilepsy, 10 of whom had SE. The SE cost was €8347 ± 10,773 per patient, which was higher than that for newly diagnosed epilepsy (€1998 ± 1089).Furthermore, the overall burden of expenditure per patient was higher for stroke (€6371 vs €8387) [6].

In our study, hospitalization for >7 days predicted high cost of SE. It is conceivable that SE patients requiring prolonged and complicated treatment would incur higher costs. In our study, refractoriness of SE was also related to higher costs. A previous study has highlighted the prognostic significance of duration of SE [13].

Drug default and stroke are the main causes of SE in western countries, whereas in India, CNS infections are the leading cause and may account for the high proportion of generalized or secondarily generalized SE [2,14]. SE patients requiring MV have respiratory suppression due to antiepileptic drugs, primary underlying pathology, or both. Our study did not include the cost of ventilator. Ventilators are provided either free or at a subsidized cost in government hospitals in India. Certain departments in our institute charge INR 700 per day ($10.9) for a ventilator. If we include this cost in our analysis, the median cost of SE will increase by 19.8% (INR 24,800, $386.12, or €343.91) than the calculated cost. Ventilated patients represent a special group that often requires multiple antibiotics, frequent biochemical and microbiological investigations, and therapies for comorbidities, which increase the cost for ventilated patients.

In previous studies from the US and Germany, median inpatient cost of SE was $18,834 and €4702 per admission, respectively. These values were approximately 20 times higher than in our study. In these reports, data had been extrapolated to the entire country's population ($4 billion in the US and €83 million in Germany). Such extrapolation in Indian patients is not practical considering the socioeconomic differences, wide variation in hospital care costs, and availability of resources and expertise. Our results may reflect the cost of SE in a government hospital. In addition, we included only the cost paid in our hospital, which may underestimate the total cost incurred by a patient. Our calculations do not include the cost paid in referring hospitals, investigations, and out-of-pocket treatment expenses. We have not calculated the indirect cost of SE, which could be assessed by mortality (34.5%) and disability (mRS, 48.2%). Calculation of indirect cost can be more complicated, therefore, providing accurate and objective data may not be possible for all patients. The predictors of death in SE include duration of seizure, age of onset, and etiology [2,11]. Such calculations may be easier in countries where healthcare is institutionalized and/or restricted to particular organizations. In India, the healthcare system is more heterogeneous. In the absence of a well-organized insurance system, 80% patients have to pay out of their pockets for healthcare [15]. Private healthcare in India is diverse and ranges from large corporate hospitals to small hospitals and private medical practice. The government contributes to only 20% of the national health expenditure [15].

The present study is limited by referral bias of more serious patients with a high proportion of CNS comorbidities and the inability to calculate indirect cost of SE. Our results may reflect the cost of SE in government hospitals in India. Additional prospective studies are warranted to calculate the direct and indirect cost of SE and identify measures to reduce them without compromising on the quality of care.

Conflict of interest

There is no conflict of interest to declare.

Financial support

None

Acknowledgments

We acknowledge Prof. Arvind Mohan, Director, Institute of Management Sciences, University of Lucknow, India for his advice in the formulation of this study. We also acknowledge the assistance of Mr. Rakesh Nigam and Mr. Deepak Kumar Anand for secretarial help. Language editing support for this manuscript was provided by Cactus Communications and funded by Sanofi (India).

References

[1] Hesdorffer DC, Logroscino G, Cascino G, Annegers JF, Hauser WA. Incidence of status epilepticus in Rochester, Minnesota, 1965–1984. Neurology 1998;50:735–41. PubMed PMID: 9521266.
[2] DeLorenzo RJ, Hauser WA, Towne AR, Boggs JG, Pellock JM, Penberthy L, et al. A prospective, population-based epidemiologic study of status epilepticus in Richmond, Virginia. Neurology 1996;46:1029–35. PubMed PMID: 8780085.
[3] Misra UK, Kalita J, Nair PP. Status epilepticus in central nervous system infections: an experience from a developing country. Am J Med 2008;121:618–23. http://dx.doi.org/10.1016/j.amjmed.2008.02.012.
[4] Trinka E, Höfler J, Zerbs A. Causes of status epilepticus. Epilepsia 2012;53:127–38. http://dx.doi.org/10.1111/j.1528-1167.2012.03622.x.
[5] Penberthy LT, Towne A, Garnett LK, Perlin JB, DeLorenzo RJ. Estimating the economic burden of status epilepticus to the health care system. Seizure 2005;14:46–51. PubMed PMID: 15642500.

[6] Strzelczyk A, Knake S, Oertel WH, Rosenow F, Hamer HM. Inpatient treatment costs of status epilepticus in adults in Germany. Seizure 2013;22:882–5. http://dx.doi.org/10.1016/j.seizure.2013.08.003.
[7] Kortland LM, Knake S, Rosenow F, Strzelczyk A. Cost of status epilepticus: a systematic review. Seizure 2015;24:17–20. http://dx.doi.org/10.1016/j.seizure.2014.11.003.
[8] Rossetti AO, Bleck TP. What's new in status epilepticus? Intensive Care Med 2014;40:1359–62. http://dx.doi.org/10.1007/s00134-014-3363-z.
[9] Rossetti AO, Logroscino G, Milligan TA, Michaelides C, Ruffieux C, Bromfield EB. Status Epilepticus Severity Score (STESS): a tool to orient early treatment strategy. J Neurol 2008;255:1561–6. http://dx.doi.org/10.1007/s00415-008-0989-1.
[10] Banks JL, Marotta CA. Outcomes validity and reliability of the modified Rankin scale: implications for stroke clinical trials: a literature review and synthesis. Stroke 2007;38:1091–6. Epub 2007 Feb 1.
[11] Towne AR, Pellock JM, Ko D, DeLorenzo RJ. Determinants of mortality in status epilepticus. Epilepsia 1994;35:27–34. PubMed PMID: 8112254.
[12] Parikh CR, Karnad DR. Quality, cost, and outcome of intensive care in a public hospital in Bombay, India. Crit Care Med 1999;27:1754–9. PubMed PMID: 10507594.
[13] Heafield MT. Managing status epilepticus. New drug offers real advantages. BMJ 2000;320:953–4. PubMed PMID: 10753129; PubMed Central PMCID: PMC1117894.
[14] Kalita J, Nair PP, Misra UK. A clinical, radiological and outcome study of status epilepticus from India. J Neurol 2010;257:224–9. http://dx.doi.org/10.1007/s00415-009-5298-9.
[15] Jayaram R, Ramakrishnan N. Cost of intensive care in India. Indian J Crit Care Med 2008;12:55–61. http://dx.doi.org/10.4103/0972-5229.42558.