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Original Research Article

Clinical Features and Outcome of Refractory Status Epilepticus Patients in an Eastern Indian Tertiary Care Hospital

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Abstract

Introduction: Refractory status epilepticus is defined as the status epilepticus which is refractory to two intravenous anti-epileptic drugs, one of which is a benzodiazepine. RSE occurs in 23–43%, this progression being time dependent with early management being advocated to achieve control.

Methods: The study included the adult patients of convulsive refractory status epilepticus admitted at the Neurology, General Medicine and Surgical intensive treatment units of Calcutta National Medical College, Kolkata, between 1st January to 31st August 2018. The patient's demographic data, medical history, treatment received and outcome were documented. We titrated all the drugs to the suppression of the seizure activity. The data are presented according to the treatment type [general anesthesia and antiepileptic drugs], and according to the outcome [favorable (modified Rankin Score or mRS<2), and unfavorable (mRS≥2)] and analyzed by univariate and subsequent multivariate analysis. Statistical analysis was done using SPSS version 22.0 software.

Results: 24 patients were included in the study, 62.5% being males. Inflammatory central nervous system diseases followed by stroke were the commonest causes of convulsive refractory status epilepticus. Mortality rate was 25% and 41.67% had the favorable outcome. Multivariate analysis identified complex partial status epilepticus [Adjusted Odds Ratio=7.6 (95% CI=1.5-54.4), p=0.04], partial onset seizures [Adjusted Odds Ratio=9.8 (95%CI=1.4-69.34), p=0.034 and hyponatremia [Adjusted Odds Ratio=7.7 (95% CI=1.32-53.37), p=0.037) as the factors responsible for failure of control of convulsive refractory status epilepticus by antiepileptic drugs alone. The need for GA was associated with unfavorable outcome [Adjusted Odds Ratio=11.7 (95% CI=1.22-125.31), p=0.037]. Patients with lower Glasgow coma score and higher Status Epilepticus Severity Score at the time of admission in intensive treatment units, those with longer time being elapsed between seizure onset and hospital admission had significant higher incidence of need for general anaesthesia and the unfavorable outcome.

Conclusion: The etiology of convulsive refractory status epilepticus does not affect the refractoriness and outcome, which are more dependent on the Glasgow coma score, Status Epilepticus Severity Score at admission and the time gap between seizure initiation and hospital admission.

Keywords: Epilepticus Severity Score; hyponatremia; modified Rankin Score.

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Introduction

Status epilepticus (SE) is defined as the seizure that persists for a sufficient length of time or is repeated frequently enough that recovery between attacks does not occur. Since majority of seizures are brief, a seizure persisting for more than 5 minutes, may not remit spontaneously. Recent SE treatment

protocols have used a 5-minute definition to minimize the risk of seizures lasting for 30 minutes, and the adverse outcomes associated with the needless optimism of spontaneous remission [1]. Refractory SE (RSE) is defined as the SE which is refractory to two intravenous anti-epileptic drugs (AEDs), one of which is a benzodiazepine. Some authorities have also defined RSE on the basis of the duration of seizure for 1 or 2 hours [2]. Super-refractory SE (SRSE) is defined as status epilepticus that continues for 24 hours or more after the use of anesthetic therapy, including the cases in which SE recurs on weaning of anesthesia [3]. RSE occurs in 23–43% and SRSE occurs in 12.2–22% of the patients with SE, this progression being time dependent with early management being advocated to achieve control [4,5]. SE has been classified into 9 types- epilepsia partialis continua, supplementary motor area, aura continua, dyscognitive focal (psychomotor, complex partial), tonic–clonic, absence, myoclonic, tonic, and subtle SE [6]. The short-term mortality of RSE is approximately three times higher compared to non-refractory SE [7]. The common causes of RSE are potentially fatal underlying diseases like encephalitis, meningitis (pyogenic, tubercular, or fungal), massive stroke, and rapidly progressive primary brain tumors [7]. In intensive treatment units (ITUs), individuals admitted for other reasons may develop subclinical ictal episodes, continuous electroencephalogram (EEG) monitoring being essential for their diagnosis. These events are classified as non-convulsive status epilepticus (NCSE). It is estimated that NCSE represents between 25- 50% of all SE cases, and various publications report the occurrence of NCSE in 10% of comatose patients [8]. New-onset RSE (NORSE) is a rare condition characterized by the occurrence of a prolonged period of refractory seizures with no readily identifiable cause in previously healthy individuals. Autoimmune encephalitis (paraneoplastic or non-paraneoplastic) and unidentified viral infections are the most commonly identified cause of NORSE; however, half of these patients remain cryptogenic. Outcome of NORSE patients is generally poor and epilepsy develops in most patients on follow-up [9]. During seizures, the receptors on the surface of the axons are in a highly dynamic state, moving onto externalization, away from internalization along the axonal membrane. This receptor trafficking intensifies during SE, and the overall effect is a reduction in the number of functional γ-aminobutyric acid (GABA) receptors and increase in the number of glutaminergic receptors on the cell surface affected in the seizure discharge. Since GABA is the principle inhibitory transmitter, reduction in its receptor density is an important reason for persistent seizures and ineffectiveness of GABAergic drugs (benzodiazepines or barbiturates) [10].

In this retrospective study, we primarily aimed to describe the experience of RSE management and to compare outcomes according to the etiology and semiology of RSE; and secondarily to determine the predictors of short-term functional prognosis.

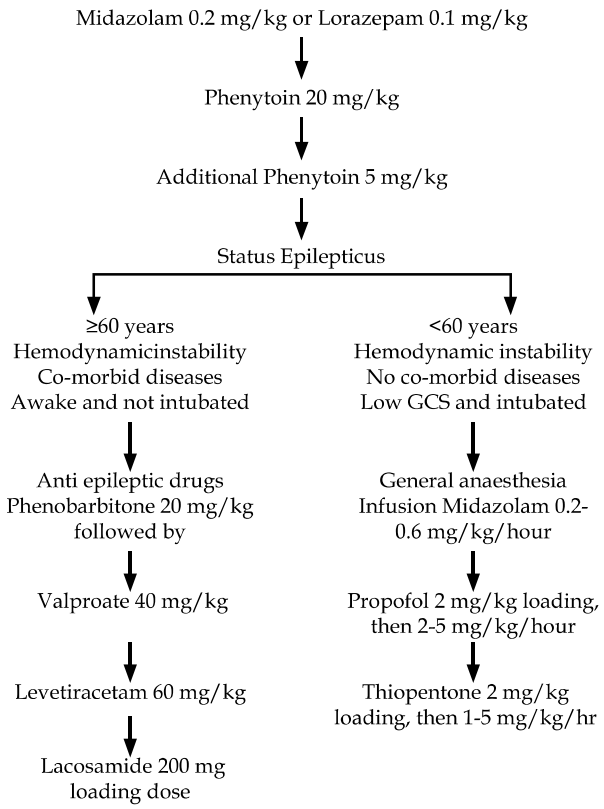
Methods and Materials

The study included the adult patients of convulsive RSE admitted at the Neurology, General Medicine and Surgical ITUs of Calcutta National Medical College, Kolkata, between 1st January to 31st August 2018. We defined RSE as SE refractory to first-line (benzodiazepines-lorazepam/ midazolam) and second-line (phenytoin) AEDs. The patient's demographic data (age, sex) and medical history (acute/chronic, neurological/non-neurological) were documented. Their paraclinical data from the first 24 hours after the onset of SE including serum sodium, calcium and glucose levels, rectal temperature, and CSF variables were analyzed. The status epilepticus severity score (STESS) components (age, history of seizures, level of consciousness and worst ever seizure) [11], and the treatments received were recorded. Finally, we analyzed outcome measures including duration of SE, short term re-occurrence of epileptic activity within 24 hours after termination of SE, length of stay in hospital and in the ITU, in-patient mortality, and the ability to regain independence in activities of daily living at one month as defined by a modified Rankin scale (mRs) score ≤2. Since the prognosis of complex partial SE (CPSE) and generalized convulsive SE (GCSE) differ, subgroup analysis of these two types of SE with regard to outcome measures was performed. STESS ranges from 0 to 6, and higher values indicate more severe derangement. Generally, a nonaggressive management was used in patients with low scores, and in patients with high scores (>2 points), deep sedation was performed. Since we did not have the facility of continuous video EEG monitoring in any of our ITUs, we titrated all the drugs to suppression of the seizure activity, instead of titrating to the achievement of a 50/50 burst suppression pattern on EEG (50% burst and 50% suppression) for at least 24 hours, as used in other studies.

Statistical analysis- We used SPSS version 22.0 (IBM Corp, Armonk, New York) for processing

and analysis of our data. All data were analyzed for normality, and appropriate statistical modeling was used accordingly. A univariate analysis was performed with descriptive statistics: proportion comparison for categorical variables with Fisher exact test and mean differences for quantitative variables with students -test. For statistical significance, a two-tailed value <0.05 was considered significant. The data are presented according to the treatment type [general anesthesia (GA) and antiepileptic drugs or AED], and according to the outcome [favorable outcome (modified Rankin Score or mRS<2), and unfavorable outcome (mRS≥2)]. We then performed a multivariate analysis using a forward stepwise logistic regression. The dependent variable was functional prognosis as determined by mRS one month after diagnosis of RSE dichotomized to good functional outcome (mRS≤ 2) and poor functional outcome (mRS> 2). In the multivariate model we included those factors with p values<0.25 and independent variables with relevant clinical significance that explained the functional prognosis. The results of the multivariate model are presented as adjusted odds ratio (AOR) with their respective confidence interval (95% CI) for variables with values<0.05.

The algorithm of SE management followed in the cases in the study-



Results

The study comprised of 24 patients.

Table 1: shows the demographic characteristics of the patients in the study.

Demographic characteristics	N=24
Mean Age (years)	47.8 (27.5)
Sex (male)	15 (62.5)
Mean GCS on admission to the ITU	10.1 (4.2)
Mean STESS	3.5 (2.0)
Mean time since seizure started (hours)	2.5 (1.6)
Etiology of RSE	
1) Stroke	
Hemorrhagic stroke	4 (16.67)
Ischemic stroke	1 (4.17)
2) Inflammatory CNS disease	
Encephalitis	2 (8.33)
Tubercular Meningitis	2 (8.33)
Multiple sclerosis	1 (4.17)
Neurocysticercosis	1 (4.17)
3) Traumatic brain injury	4 (16.67)
4) Anoxic encephalopathy	1 (4.17)
5) Autoimmune encephalopathy	3 (12.5)
6) Brain tumor	1 (4.17)
7) Preexisting epilepsy flare	3 (12.5)
8) Cortical dysplasia	1 (4.17)

[Data are number (%), mean (standard deviation or SD); GCS: Glasgow Coma Scale; STESS: Status Epilepticus Severity Score; CNS: central nervous system]

Two patients of stroke, 1 patient of encephalitis, and 1 patient of preexisting epilepsy flare were admitted at the General Medicine ITU. 3 patients of traumatic brain injury and the patient of anoxic encephalopathy following cardiac arrest during appendicectomy operation were admitted at the Surgery ITU. Rest patients were admitted at the Neurology ITU. 1 patient of encephalitis tested positive for herpes virus, but the other patient had negative serologies for herpes, Japanese encephalitis and chikungunya viruses. Among the 3 patients with autoimmune encephalopathy, 2 were N-methyl D-aspartate receptor antibody positive and 1 had Hashimoto encephalitis (Anti-TPO positive) (Table 1).

Table 2: Univariate analysis of factors associated with difficulty in controlling RSE, hence the need for general anesthesia (GA).

Factors	No. of patients needing only AEDs (N=15)	No. of patients needing GA (N=9)	Odds ratio	95% CI	p value
Age>60 years	1	4	11.2	0.99-125.64	0.047
Sex (male)	9	6	0.75	1.33-4.22	1
Mean (SD) GCS	9.5 (2.1)	7.1 (1.2)			0.005
Mean (SD) time since seizure started (hours)	1.2 (0.5)	2.9 (1.0)			0.0001
Mean (SD) STESS score	3.0 (0.845)	4 (0.86)			0.0107
Neuroinfection	1	3	7	0.59-81.68	0.25
Stroke	4	1	0.343	0.32-3.68	0.614
Encephalopathy	1	3	7	0.59-81.68	0.25
Previous epilepsy	2	1	0.8125	0.063-10.87	1
Brain tumour	0	1	Infinity		0.374
Seizure types-					
CPSE (N=7)	2	5	8	1.11-59.21	0.04
GCSE (N=17)	13	4			
Partial onset seizure (N=11)	4	7	9.62	1.37-67.24	0.03
Generalized onset seizure (N=13)	11	2			
Recurrence of seizures (N=6)	1	5	17.5	1.55-196.32	0.01
Hyponatremia	3	6	8	1.22-52.24	0.036
Hypoglycemia	2	4	5.2	0.71-32.89	0.15
Sepsis	2	3	3.25	0.42-24.84	0.32
Shock requiring inotropes	1	3	7	0.59-81.68	0.258
Mean (SD) days of ITU stay	5.5 (1.0)	10.2 (4.4)			0.0006
Mortality	1	5	17.5	1.55-196.32	0.015

The seizures were partial onset in 11 patients, 7 remained as CPSE and 4 progressed to generalization. Rest 13 patients had generalized seizures without partial onset. The following patients needed GA administration- 3 patients of hemorrhagic stroke, 1 patient of encephalitis, 2 patients of tubercular meningitis, 1 patient of anoxic encephalopathy and 2 patients of traumatic brain injury. Table 2 showed that older patients, patients with lower GCS and higher STESS score at the time of admission in ITUs, and those with longer time being elapsed after seizure onset had significant higher need for GA. Patients needing GA had a significantly higher incidence of hyponatremia and longer ITU stay. Multivariate analysis identified CPSE [AOR=7.6 (95%CI=1.5-54.4), p=0.04], partial onset seizures [AOR=9.8 (95%CI=1.4-69.34), p=0.034], and hyponatremia [AOR=7.7 (95% CI=1.32-53.37), p=0.037) were the factors responsible for failure of control of RSE by AEDs alone. The mean duration of ITU stay and mortality was significantly higher among patients needing GA. Recurrence of seizures within 24 hours after termination of RSE was significantly more common among patients needing GA. However, none of these recurrences fulfilled the definition of SE. 1 patient of each of the following diagnoses expired- hemorrhagic stroke, encephalitis, tubercular meningitis, anoxic encephalopathy, brain tumor and traumatic brain injury (Table 2).

Table 3: Univariate analysis of factors associated with unfavorable short-term functional outcome

Factors	Favorable outcome (N=10)	Unfavorable outcome (N=14)	Odds ratio	95% CI	p value
Age>60 years	4	1	8.66	0.789-95.09	1.22
Sex (male)	8	7	0.25	0.03-1.6	0.2
Mean (SD) GCS	9.4 (2.4)	6.9 (3.1)			0.04
Mean (SD) time since seizure started (hours)	1.5 (0.6)	3.0 (1.5)			0.069
Mean (SD) STESS score	2.8 (0.68)	4.2 (0.78)			0.002

Neuroinfection	2	2	0.67	0.08-5.75	1.0
Stroke	2	3	1.09	0.14-8.12	1.0
Encephalopathy	2	2	0.67	0.08-5.75	1.0
Previous epilepsy	2	1	0.31	0.02-9.99	0.55
Brain tumour	0	1	Infinity		1.0
Seizure types-					
CPSE (N=7)	3	4	9.93	0.15-5.54	1.0
GCSE (N=17)	4	10			
Partial onset seizure (N=11)	7	7	1.5	0.29-7.75	0.69
Generalized onset seizure (N=13)	6	7			
Recurrence of seizures (N=6)	1	5	1.6	0.23-11.08	1.0
Hyponatremia	4	5	0.83	0.15-4.43	1.0
Hypoglycemia	2	4	1.6	0.23-11.08	1.0
Sepsis	2	3	0.38	0.05-2.92	0.61
Shock requiring inotropes	2	2	0.66	0.08-5.74	1.0
Need for GA	1	8	12	1.17-122.27	0.03
Mean (SD) days of ITU stay	5.9 (1.5)	10.9 (2.8)			<0.0001

[The term 'Encephalopathy' in tables 2 and 3 included anoxic and autoimmune encephalopathy]

The following patients had the unfavorable outcome- 1 patient of hemorrhagic stroke, 1 patient of encephalitis, 2 patients of tubercular meningitis, 1 patient of anoxic encephalopathy and 2 patients of traumatic brain injury. Table 3 showed that patients with lower GCS and higher STESS score at the time of admission in ITUs, those with longer time being elapsed between seizure onset and hospital admission, longer mean ITU stay and those needing GA had significant higher incidence of unfavorable outcome. Multivariate analysis identified need for GA [AOR=11.7 (95% CI=1.22-125.31), p=0.037] as the factor responsible for the unfavorable outcome. However, recurrence of seizures had no effect on the final outcome (Table 3).

Discussion

The clinical characteristics of refractory status and risk factors of the condition are poorly understood; therefore current management approaches are still unsatisfactory [12]. In our study, only 12.5% patients had a past history of epilepsy. Others had an acute neurologic lesion- neuroinfections (25%), stroke (20.84%) and traumatic brain injury (16.67%) being the leading causes. Hernandez [8] also described that acute neurological lesions were the most common causes for SE (75.1%), with stroke and central nervous system infection being the principal etiologies. However, lower percentage of acute neurologic causes of SE have been reported in the literature; around 33–50% of SE cases occur in patients without past medical history of epilepsy, stroke (20–36%), head trauma (1–26%), metabolic alterations or drug withdrawal (7–26%), central nervous system infections (3–14%), or tumors (5–24%) being the foremost causes [13,14]. Age and sex were not significant determining factors for the need of GA and unfavorable outcome. In univariate analysis, although patients aged>60 years had significantly higher chance of needing GA, multivariate analysis did not confirm it as a significant independent variable. Holtkamp [12] also demonstrated that distribution of age and sex was not significantly different between their two study groups- SE and RSE. Misra's Indian study [15] too showed that there was no difference between the groups of SE and SRSE patients with respect to age (p = 0.09), and gender (p = 0.19). However, age ≥60 year was independently associated with unfavorable short-term functional outcome [8] and also poorer outcome at 1 year [16].

Our institution being a tertiary referral center, the transfer and admission of patients to the ITUs with generalized and partial SE are often delayed. Our study showed that the mean time elapsed between the start of the seizures and admissions at the ITUs were significantly related to the lack of control of the RSE by AEDs alone and also the unfavorable outcome. In their study, Hernandez [8] also described unfavorable short-term outcome for patients with seizure duration>10 hours, however, the values were not significant in their study. But Giovannini in their one-year Italian prospective study of RSE showed that treatment becomes less effective with increasing duration of RSE [17]. Also,

in Towne's study [18], when the patients were divided into two groups, the group with SE lasting < 1 hour had a lower mortality as compared with seizure duration ≥1 hour. Longer RSE duration was associated with poorer functional long term outcome in Madzar's study [19]. In our study, the mean GCS was significantly associated with the need of GA and unfavorable outcome, as showed in multiple other studies [8, 20]. Higher STESS scores were also strongly associated with the need for GA and the unfavorable outcome, as also demonstrated by Misra [15]. Aukland [21] demonstrated that the in-hospital mortality correlated highly significantly with STESS, when the optimal cut-off was 4. With respect to long-term outcome, STESS correlated significantly with the overall mortality though with lower odds ratios. When considering only the survival of the acute phase, the STESS components "level of consciousness" (at admission), "coma" as worst seizure type, and "age" had statistically significant association with mortality [21].

In our study, the etiology of the RSE did not affect the need for GA and the unfavorable outcome. The etiologies having no effect on the long term outcome were also described by Kantanen [16] and Madzar [19]. Sutter [22] found only hypoxic/ anoxic brain injury and intracranial tumour to negatively affect long term outcome. In our study, 1 patient each of anoxic encephalopathy and brain tumour expired. Hernandez [8] found that stroke and acute neurological lesions were associated with poor short-term outcome in univariate analysis, but multivariate analysis failed to confirm either of the factors as significant independent variables. CPSE, GCSE with partial onset and GCSE without partial onset were 25.92%, 16.67% and 54.16% in our study compared to 49.4%, 19.3% and 18.1% in Holtkamp's [12] study. CPSE and partial onset seizures were associated with significantly higher risk of need for GA, but not for the unfavorable outcome. Holtkamp [12] described that subgroup analysis of outcome measures with regard to CPSE and GCSE showed that the duration of seizures was significantly longer in CPSE (205.2 hours) compared with GCSE (46.8 hours; $p<0.05$) whereas all other measures were not significantly different between the groups. Recurrence of the seizures after termination of RSE occurred more frequently after weaning from GA, and did not predict the outcome. Holtkamp [12] described that in those patients surviving SE, recurrence of epileptic activity was seen significantly more often with RSE (45.4%) compared with non-refractory SE (6.5%). Para clinical factors like hypoglycemia, sepsis and shock requiring inotropes were non-significantly higher among patients needing GA and those with unfavorable outcome. However, hyponatremia was significantly higher among patients needing GA. In Holtkamp's study [12], hyponatraemia measured in the first 24 hours after onset of SE was significantly associated with refractoriness. Clinical and experimental data have shown the proconvulsive properties of hyponatraemia [23]. Hence, there is need to correct hyponatraemia in all patients with SE with due consideration of the risk of severe neurological deficits while reloading serum sodium too rapidly. In our study, the mean days of ITU stay was significantly higher among those who needed GA and was associated with the unfavorable outcome. Misra [15] described that in their study, the incidence of VAP was higher among the patients of SRSE compared to patients of RSE, but the incidence of arrhythmia, hypotension and sepsis were not significantly different among the two groups. Holtkamp [12] described that the length of stay in the neuro-ITU was significantly longer in RSE (median 16.5 days) compared with non-refractory SE (median 2 days). Misra [15] described that the patients with SRSE had longer duration of ICU stay ($p=0.002$), and mechanical ventilation ($p<0.01$) compared to RSE. Hocker [24] also described poorer outcome of patients of RSE needing longer duration of ventilation and Sutter [22] described poorer outcome for patients needing cardiopulmonary resuscitation.

Mortality was 25% in our study, compared to 22.5% (Hernandez) [8], 38% (Sutter) [22] and 12.65% (Holtkamp) [12]. Favorable outcome at first month follow-up was seen in 41.67% patients in our study, compared to 48.4% (Hernandez) [8], and 35.7% (Misra) [15]. Studies of RSE (convulsive and non-convulsive) with cases numbering less than 100 have been published with a similar long-term outcome—recovery to baseline in 36%, neurological deficit in 23%, and death in 41% [16]. Another review found in the assessment of the long-term outcomes of 596 convulsive RSE and SRSE cases, approximately 35% of cases reached baseline neurological status, 35% died, and 30% had variable neurological deficits. The duration at which outcome was assessed varied from months to years [25].

According to the literature, coma induction titrated to attain EEG burst suppression pattern were associated with a significant lower incidence of breakthrough seizures, suggesting that the burst suppression is produced by the effect over the GABA receptors of the cortical-thalamic pathways, generating a cortical synchronization

that could explain the control of seizure activity [26]. However, the non-availability of continuous video EEG monitoring at all the ITUs included in the study prohibited us from undertaking the coma induction. The other limitations of our study were small sample size, lack of data on long-term clinical outcomes including quality of life, the retrospective nature of the analysis which can be subjected to bias, and the reported cohort being from a single centre.

Conclusion

It needs to be emphasized what this study adds- 1) CPSE and partial onset semiology RSE is more difficult to control with AEDs alone. 2) Patients with RSE should to be checked for hyponatremia, and meticulous correction to be done, if needed. 3) Etiology of the RSE does not affect the refractoriness of the seizures and the outcome. 4) The GCS, STESS scores at admission and the time elapsed from the seizure onset to treatment initiation determines the refractoriness and the final outcome.

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