



Prognosis and predictors of outcome of refractory generalized convulsive status epilepticus in adults treated in neurointensive care unit



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ABSTRACT

Objective: To evaluate the etiological profile, clinical characteristics and outcome of patients with refractory generalized convulsive status epilepticus treated in Neurological Intensive Care Unit (NICU).

Methods: In this open cohort study, data of 126 patients, aged 18 years and above, with convulsive status epilepticus (SE) admitted in NICU was collected. Status epilepticus was defined as seizures lasting for more than five minutes without regaining consciousness. Refractory SE (RSE) was defined as SE refractory to 2 antiepileptic drugs and requiring anesthetic agents for seizure control. Survival and regression analysis were done to analyze the outcome and factors predicting outcome respectively in the study population. **Results:** Out of 126 patients, 81 patients had non-refractory status epilepticus (NRSE); 45 (35.7%) had RSE. Acute symptomatic etiology was noted in 58.6% of entire cohort. Significantly higher percentage of patients with RSE had an etiology of CNS infections than NRSE group (44.4% vs. 23.5%; $P=0.0171$). Amongst the CNS infections, viral encephalitis was significantly higher in RSE than NRSE patients (31% vs. 6.2%; $P=0.0004$). All the patients with RSE required mechanical ventilation. Overall mortality was 19%. The mortality in RSE was 42% (19 out of 45), significantly higher when compared to NRSE where only 6% (5 out of 81) died. On logistic regression, the only predictor of death was fever with an odds ratio of 8.55 ($P=0.024$).

Conclusion: CNS infections, especially viral encephalitis and complications of mechanical ventilation were significantly higher in adult RSE patients. Although mortality is higher in adult patients with RSE, etiology does not contribute to mortality; however fever predicts mortality in these patients. Aggressive management of underlying etiology and prevention of systemic complications may improve outcome in adult RSE patients.

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1. Introduction

Status epilepticus (SE) is a life threatening neurological emergency that warrants effective and immediate management. The incidence of SE among adults is approximately 17.1 per 100,000 people per year [1]. In 23–43% of the patients [2], SE persists despite administration of anti-epileptic drugs (AED) and hence named as refractory status epilepticus (RSE) [3–7]. Refractory SE in adults has been attributed to encephalitis, brain tumors, cerebro-vascular disease (CVD) and low levels or withdrawal of anti epileptic drugs

(AED) [4,8–12]. Risk factors for RSE include new onset seizures, older age, underlying etiology such as encephalitis [13] and duration of SE [14].

Refractory SE may persist for weeks together and an increased duration of SE has previously been associated with poor prognosis [15]. Mortality in RSE is significantly higher, mostly attributable to age, underlying etiology and impaired consciousness at presentation [15–19]. Although guidelines for the management of SE [20,21] in adults are well established, the optimal treatment for RSE remains elusive; probably because studies till date have been either small retrospective reviews or prospective cohorts without a control group. Nearly 40% of patients with RSE die, mechanical ventilation is required in almost all cases of RSE and a longer duration on mechanical ventilation has been associated with mortality in these patients [22], with pneumonia and hypotension being the most common complications observed.

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Table 1
Demographic and etiological comparison between refractory status epilepticus (RSE) and non-refractory status epilepticus (NRSE).

Variable	RSE (n = 45)	NRSE (n = 81)	P-value
Age (years)	35.7 ± 16.7	40.4 ± 16.6	0.883
Gender (number of Men)	26	52	0.301
Past history of epilepsy (number of patients)	13	29	0.279
Duration on mechanical ventilation (number of days)	6.91 ± 9.0	0.89 ± 3.0	<0.0001
Ventilatory care (number of patients)	45	11	<0.001
Length of stay in NICU (number of days)	7.24 ± 9.8	3.77 ± 3.2	<0.0001
Length of stay in hospital (number of days)	10.2 ± 13.1	7.9 ± 3.9	<0.0001
<i>Etiological profile (number of patients)</i>			
Known epileptic/anti epileptic drug withdrawal (number of patients)	4	15	0.1967
Alcohol withdrawal (number of patients)	3	1	0.1297
Vascular (number of patients)	8	25	0.1399
Metabolic (number of patients)	1	6	0.4200
Idiopathic (number of patients)	5	9	1.0000
Gliosis (number of patients)	3	5	1.0000
<i>CNS infections (number of patients)</i>			
TB meningitis (number of patients)	20	19	0.0171
Cysticercosis (number of patients)	4	3	0.2470
Viral encephalitis (number of patients)	1	7	0.2573
Focal cerebral calcification (number of patients)	14	5	0.0004
	1	4	0.6541

Note: Data is expressed as mean ± standard deviation or absolute numbers. $P < 0.05$ is considered as statistically significant.

Ongoing RSE for several weeks becomes demanding both on the treating physician and the family of the patient, particularly in countries with limited resources. A detailed understanding of the clinical spectrum, risk profile and management of RSE patients in comparison to non-refractory SE (NRSE) patients may help predict and probably improve outcome in RSE patients. The aim of the current study was to evaluate the clinical characteristics, etiology and outcome of patients with RSE treated in the Neurological Intensive Care Unit (NICU) of a tertiary referral center.

2. Methods

A retrospective analysis of consecutive adult patients with convulsive SE undergoing treatment at Krishna Institute of Medical Sciences, a tertiary referral center, located in Secunderabad, South India was done from December 2005 to August 2013. Patients with convulsive SE aged 18 years and above, admitted to the NICU were included in the study. The patients with myoclonic SE, psychogenic SE, complex partial SE, absence SE, simple partial SE and those with non-convulsive SE were not included in the study.

Status epilepticus was defined as seizures lasting for more than five minutes without regaining consciousness [23]. RSE was defined as SE resistant to one first line, and one second line AED, requiring general anesthesia (GA) [11]. Duration of RSE was defined as the time period between the initiation and successful discontinuation (without seizure recurrence) of anesthetic drugs to manage RSE [24].

Etiology of SE was classified as acute symptomatic, remote symptomatic, those with pre-existing epilepsy, and idiopathic (cause undetermined) [24]. Acute symptomatic group included patients with CNS infections (encephalitis, tuberculosis, and neurocysticercosis), acute cerebrovascular insults (ischemic/hemorrhagic stroke, cortical sinus venous thrombosis), and those with metabolic etiologies. The diagnosis of CNS infection was based on magnetic resonance imaging features of the brain, CSF analysis including PCR and other associated systemic features.

All the patients received treatment according to the established guidelines for the management of SE [14,20]. The data collected included, demographic variables, etiology, history of epilepsy, AED history, details of SE, hospital stay, duration on mechanical ventilation, length of stay in NICU, complications of mechanical ventilation and outcome of the patients including relevant investigations. This study was reviewed and approved by the local ethics committee.

Statistical analysis: After testing for the normal distribution of the data, the study population was divided into with RSE and NRSE groups. Differences between the groups for continuous variables were analyzed using independent student *t*-test, accounting for variance amongst group using Levene's test for equality of variance. Categorical variables were analyzed using chi-square test. A $P < 0.05$ was considered significant. Variables that were significantly different between the groups were included in logistic regression model to help evaluate predictors for death. Mortality between the groups was compared using life tables survival analysis. Statistical Package for Social Sciences (SPSS, ver. 17.0, IBM computers, New York, USA) was used for all statistical analysis.

3. Results

A total of 126 patients were included in the study, 81 were classified as NRSE while 45 (35.7%) patients formed RSE group. The demographic and clinical variables analyzed are summarized in Table 1.

3.1. Etiology

In the entire cohort of 126 patients, acute symptomatic etiology accounted for 58.6% (74/126); amongst acute symptomatic, central nervous system (CNS) infections accounted for 31% (39/126). Significantly higher percentage of patients with RSE had an etiology of CNS infections than NRSE group (44.4% vs. 23.5%; $P = 0.0171$). On further analysis, amongst the CNS infections, the incidence of viral encephalitis was significantly higher in RSE than in NRSE patients (31% vs. 6.2%; $P = 0.0004$). The other infections causing SE were CNS tuberculosis, neurocysticercosis, and calcified granulomas related to a possible remote infection; vascular etiology was the cause of SE in 26% (33/126) of the population. Vascular and metabolic etiology was noted more frequently in NRSE. One patient in NRSE group had a focal cortical dysplasia, whereas one patient in RSE group had etiology of possible febrile infection related encephalopathy with SE (FIRES). The etiological profile of the study population is summarized in Table 1.

3.2. Course in hospital

The median survival time of RSE patients in NICU was 9.59 days, whereas patients with NRSE survived for 20.31 days. All the patients

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