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Clinical Study

Refractory Status Epilepticus: Experience in a Neurological Intensive Care Unit

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Introduction. Refractory status epilepticus (RSE) has significant morbidity and mortality, and its management requires an accurate diagnosis and aggressive treatment. *Objectives*. To describe the experience of management of RSE in a neurological intensive care unit (NeuroICU) and determine predictors of short-term clinical outcome. *Methods*. We reviewed cases of RSE from September 2007 to December 2008. Management was titrated to findings on continuous video EEG (cVEEG). We collected patients' demographics, RSE etiology, characteristics of seizures, cVEEG findings, treatments, and short-term outcome. Control of RSE was to achieve burst suppression pattern or electrographic cessation of ictal activity. *Results*. We included 80 patients; 63.8% were in coma, 25% had subclinical seizures, and 11.3% had focal activity. 51.3% were male and mean age was 45 years. Etiology was neurological lesion in 75.1%, uncontrolled epilepsy in 20%, and systemic derangements in 4.9%. 78.8% were treated with general anesthesia and concomitant anticonvulsant drugs. The control of RSE was 87.5% of patients. In-hospital mortality was 22.5%. The factors associated with unfavorable short-term outcome were coma and age over 60 years. *Conclusions*. RSE management guided by cVEEG is associated with a good seizure control. A multidisciplinary approach can help achieve a better short-term functional outcome in noncomatose patients.

1. Introduction

Status epilepticus (SE) is a medical emergency, due to significant morbidity and mortality and requires prompt attention and adequate management. In different series, the SE mortality varies between 17 and 26%, and approximately 10 to 23% of the patients that survived presented some degree of neurological impairment [1–4]. In the Intensive Care Unit (ICU) there are two groups of patients with SE: patients with multiple episodes of clinical seizures who have various response to initial management, and there are individuals admitted for other reasons who developed subclinical ictal episodes during their stay in the ICU. The latter is classified as nonconvulsive status epilepticus (NCSE) [1, 4, 5].

It is estimated that NCSE represents between 25 and 50% of all SE cases, but in the critically ill patient this entity could have a greater incidence. Various publications report that 10% of comatose patients suffer from NCSE, being the incidence much higher in the neurocritical care unit (NeuroICU), where about 34% of patients can have altered consciousness [6–11].

Continuous video electroencephalogram (cVEEG) monitoring is a necessary tool in patients with SE to establish adequate diagnosis, classification of disease, treatment guidance, and followup until ictal activity suppression is reached [12–14].

It is calculated that 10 to 40% of all patients with SE evolve to a refractory status epilepticus (RSE). In general,

this progression is time dependent with early management being advocated to achieve control [15, 16]. RSE is defined as either the absence of response to a first-line antiepileptic drug (benzodiazepines) and to one or two second-line drugs (phenytoin, phenobarbital, or valproate) or persistent ictal activity despite one- or two-hour treatment. RSE has a high mortality (up to 50%) and usually requires suppression of ictal electrographic activity [1, 15, 16].

The RSE approach in the NeuroICU needs a multidisciplinary team with the participation of neurophysiologists, intensive care specialists, neurologists, and in some cases, neurosurgeons. Control of RSE demands the use of multiple anticonvulsant drugs (AEDs), high-dose sedatives, and vasopressive support. Since these medications typically induce respiratory depression and hemodynamic instability, mechanical ventilatory support and invasive monitoring are necessary [1, 15–22].

RSE management is based on case reports and experience from large tertiary-care centers. Most investigators recommend two types of management: (1) administration of sedatives to achieve elimination of electrographic ictal activity and reaching pharmacological burst suppression pattern and (2) a less aggressive alternative, without sedation, using AEDs in high doses, in a step-up approach, guided by the improvement observed by cVEEG monitoring [23–30].

We set out to investigate several aims: to describe the experience of approach and management of RSE in a NeuroICU; to compare outcomes according to the type of RSE (comatose and noncomatose); and to determine the predictors of short-term functional prognosis.

2. Patients and Methods

We conducted a retrospective study that included all patients in the NeuroICU at the Instituto Neurologico de Colombia (Medellin, Colombia), in whom the diagnosis of RSE was made between September 2007 and December 2008.

In all patients, pharmacologic treatment was guided by cVEEG monitoring. A Cadwell equipment with 32 channels and surface electrodes was used, following the protocol according to the International 10–20 System; also, electrodes were installed for electrocardiogram monitoring, surface electromyography in both deltoids, and in some cases, electrooculogram, depending on the clinical symptoms reported. The cVEEG interpretation was made by two trained neurophysiologists who sent a verbal and written report every twelve hours. Analysis was performed using Easy III (Cadwell Inc., Kennewick, WA) software, evaluating the recording, at least in three montages, modifying sensitivity and speed when necessary for the analysis.

Electrographic criteria defined by Young et al. and modified by Chong and Hirsch for diagnosing NCSE were used [31, 32]. The status epilepticus classification was performed according to clinical features: coma (ICU patient without waking who develops EER), subtle status (patient with acute electrographic seizure after initial treatment of status epilepticus), and refractory partial status (patient with electroclinical findings of refractory focal seizures).

Our group defined RSE as SE refractory to first-line (benzodiazepines) and second-line (phenytoin, phenobarbital, or valproate) AEDs. A staff conformed by NeuroICU doctors and clinical neurophysiologists defined RSE classification and management of patients according to institutional algorithm. Our therapeutic approach included general anesthesia (continuous infusion of midazolam, propofol, and/or thiopental) and concomitant AEDs (valproate, levetiracetam, topiramate, and phenobarbital, among others). For therapeutic purposes, patients' age, hemodynamic status, comorbidities, and level of consciousness as determined by the GCS [33], were considered. Patients' management algorithm is presented in Figure 1.

In those patients receiving deep sedation, the management goal was achievement of a 50/50 burst suppression pattern on EEG pattern (50% burst and 50% suppression) for at least 24 hours. Subsequently, our management protocol called for a 5%/hour dose tapering of the medication used. In those patients receiving management with only step-up AEDs, the therapeuticgoal was accomplishment of EEG control of ictal activity. In those patients with successful control of RSE, we performed cVEEG monitoring every 48 hours or before that if the patients' condition required it for evaluation of relapse of ictal activity, which we called breakthrough seizures.

We collected the following data from the medical records: patients' demographics, etiology of RSE, the Acute Physiology And Chronic Health Evaluation (APACHE) II score, Status Epilepticus Severity Score (STESS), clinical characteristics of seizures, EEG findings, treatments received, and short-term outcome. The latter was defined as in-patient mortality and ability to regain independence in activities of daily living at one month as defined by a modified Rankin scale (mRs) score ≤ 2 [34]. The APACHE II score was selected because it is a good validated indicator of underlying disease severity [35]. APACHE II score ranges from 0 to 71, and higher values indicate more severe disease state. The STESS has been suggested as a good indicator of severity of SE [36]. 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 (more than 2 points), deep sedation was performed.

2.1. Statistical Analysis. We used SPSS version 15.0 for processing and analysis of our data (Chicago, IL, 2006). 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 χ^2 association test or Fisher exact test and mean differences for quantitative variables with student's t-test or Mann-Whitney test. For statistical significance, a two-tailed P value <0.05 was considered significant.

The data are presented according to the type of RSE (coma, subtle, and partial), treatment type (general anesthesia and AED), and according to the gold of treatment (control and no control of RSE). Additionally, the cohort of patients

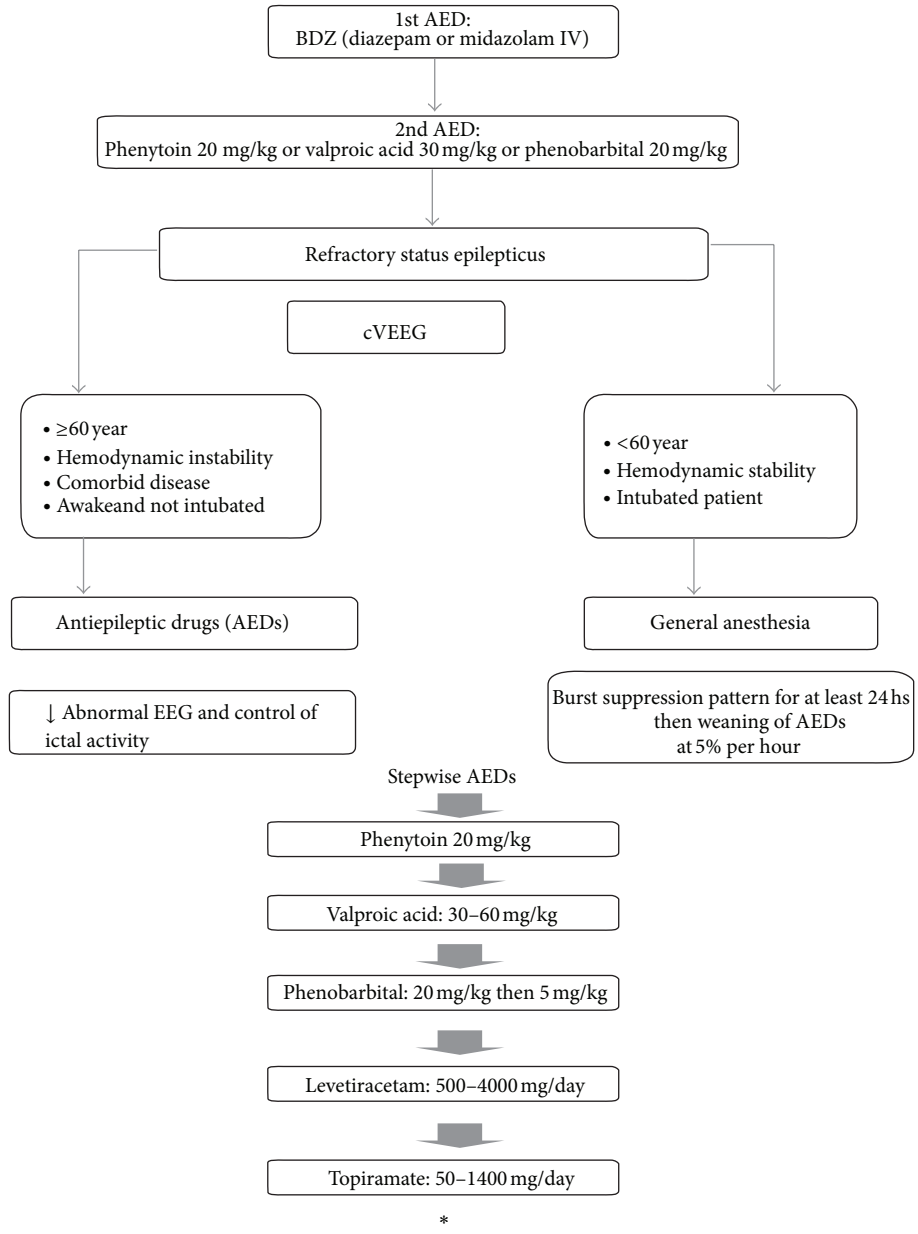

Figure 1: Treatment algorithm for RSE: guidelines from the Instituto Neurologico de Colombia.

was recategorized according to the presence or absence of coma (subtle and partial refractory state).

We then performed a multivariate analysis using a forward stepwise logistic regression (Forward Stepwise [RV] Method). The dependent variable was functional prognosis as determined by mRs one month after diagnosis of RSE dichotomized to good functional outcome (mRs $\leq$ 2) and poor functional outcome (mRs > 2). We included in the multivariate model those factors with P values <0.25. Finally we included those independent variables with relevant clinical significance that explained the functional prognosis. The results of our multivariate model are presented as odds ratio (OR) with their respective confidence interval (95% CI) for variables with P values <0.05. In addition, we included interaction terms and investigated collinearity among the covariates of interest.

3. Results

During a 15-month period, 619 patients were admitted to our NeuroICU. Of those 80 (12.9%) had RSE. Most patients were men (51.3%) with a mean age of 45 years. The most frequent clinical findings in the patients who developed RSE were altered level of consciousness (77.5%) and minor motor findings (rhythmical twitching of facial muscles, ocular muscles, or distal extremities) (30%). The most common etiology

Table 1: Demographic characteristics of patients.

Demographic characteristics	$n = 80$
Age (years)	45 (19.5)
Sex (male)	41 (51.3)
GCS on admission to the NeuroICU	10 (8–14)
APACHE II Score	15 (9–20)
STESS	4 (2–4)
Days since seizure started	3 (1.5–7)
Etiology of RSE	
Acute neurological lesion	60 (75.1)
Stroke	29 (48.3)
Hemorrhagic	17 (58.6)
Ischemic	12 (41.4)
CNS infection	9 (15)
TBI	8 (13.4)
Anoxic encephalopathy	7 (11.7)
CNS tumors	5 (8.3)
Other (intracranial hypertension syndrome, neuroleptic malignant syndrome)	2 (3.3)
Preexisting epilepsy flare	16 (20)
Systemic acute lesion	4 (4.9)

Data are number (%), mean (SD), or median (IQR).
GCS: Glasgow Coma Scale; NeuroICU: neurological intensive care unit; APACHE II: The Acute Physiology and Chronic Health Evaluation Score; STESS: Status Epilepticus Severity Score; RSE: refractory status epilepticus; CNS: central nervous system; TBI: traumatic brain injury.

of RSE was acute neurological lesion in 75.1% of the patients. The demographic characteristics of our cohort are shown in Table 1.

All the patients included in this study met NCSE criteria as defined by cVEEG monitoring and the medical staff caring for them.

The characteristics of the patients who developed RSE were different in the three study groups: RSE coma patient, subtle status, and refractory partial status. Most of these patients were comatose (63.8%), and most (94.1%) were admitted with acute neurologic injury, and its evolution developed an RSE. The second RSE group (subtle status) accounted for 25%, of which the majority (75%) had a history of epilepsy and after initial management of status epilepticus persisted with electrographic seizures. In the latter group, 11.3% of patients had partial subclinical RSE. Comatose RSE patients had the worst condition with the highest scores according to baseline characteristics (Table 2).

We found that the entire cohort of patients received benzodiazepines as first-line medication: 75% midazolam, 15% diazepam, and 10% lorazepam. In addition, we found that the second-line medications were phenytoin (76.3%), valproate (22.5%), and phenobarbital (1.2%).

We instituted profound sedation in 78.8% of patients with RSE and step-up AEDs administration in all of them. We found that for coma induction, the most frequently used medication was midazolam (87.3%), and levetiracetam and topiramate were the most frequently administered newer-generation AEDs for continuing the step-up management of RSE (97.5% and 77.5%, resp.) (Table 3). The most frequent complication associated with profound sedation use was hypotension, without significant differences between the medications used (midazolam 34.5%, propofol 32.1%, and thiopental 33.3%). One patient experienced propofol-infusion syndrome.

Those patients managed with general anesthesia required longer treatment and more medications compared with patients managed only with AEDs (Table 4). In comatose RSE, general anesthesia management was used in 90.2% of patients; the remaining comatose patients (9.8%) were treated only with AED because their base condition did not allow any aggressive treatment; of those, 2 died (40%) and additionally, a patient did not reach control (20%). When compared with the aggressive management subgroup, the mortality was 30.4%, and there was no seizure control in 10.9%.

The rate of general anesthesia management in subtle form was 85%, and a nonaggressive management was performed in the remaining (15%) because of their initial condition (nonintubated) and also a STESS less than 2. Whereas all patients with partial RSE received step-up AED only.

The median duration of cVEEG monitoring was 120 hours (IQR: 120–132). The EEG patterns during treatment induction were as follows: localized interictal epileptiform activity in 80%; periodic/pseudoperiodic generalized discharges [GPED] in 95%, and periodic/pseudoperiodic lateralized discharges [PLEDs or BiPLEDs] in 40%. According to electrographic classification of comatose RSE, 58.8% of the patients had a GED-coma pattern (Generalized Epileptiform Discharges).

RSE was successfully controlled within 3 days in 87.5% of patients, with a longer median time for those patients treated with general anesthesia compared to those who received AEDs only (Table 4). Only two patients of those who achieved successful control of RSE control presented breakthrough seizures (2.9%). The RSE control was achieved in 88.2% of patients in coma and 86.6% of the non-comatose group; 66% and 50% of patients that did not reached control of RSE died in the coma and non-coma group, respectively. The mortality in uncontrolled patients was significantly higher compared to those who achieved control of RSE (60% and 17.1%, resp., $P = 0.007$). Similarly, the no control is associated with a short-term unfavorable outcome in univariate analysis (Table 5).

In univariate analysis, we found that the only factor associated with lack of control of RSE was stroke (Table 6). In addition, our data show that patients with RSE who are comatose required longer treatment days and had higher mortality and poorer clinical outcome, in contrast to those who were non-comatose (Table 7).

Overall in-hospital mortality was 22.5%. All patients that died did so during their stay in the ICU, of which 88.9% belonged to the comatose group and the 11.1% to the noncomatose group. Mortality in the comatose group resulted from their initial neurological injury; from the non-comatose group, two patients died who were part of the subgroup of subtle state: a patient with endocarditis and

Table 2: Patient's characteristics according to RSE type.

	Coma $n = 51$	Subtle $n = 20$	Partial $n = 9$	P value
Age	48 (18.8)	33 (17.4)	53 (18.2)	0.004
GCS at NeuroICU admission	9 (7–13)	10 (8–14)	14 (11–14)	0.005
APACHE II Score	17 (12–21)	14 (7–16)	8 (3–9)	<0.0001
STESS	4 (4-4)	2 (2-2)	1 (0–2)	<0.0001
Time until treatment in NeuroICU, days	1 (0.5–7)	2 (1–6)	1 (1–5.5)	0.92
Etiology				
Acute neurological lesion	48 (94.1)	5 (25)	7 (77.8)	<0.0001
Acute systemic lesion	3 (5.9)	0	1 (11.1)	0.39
Epilepsy	0	15 (75)	1 (11.1)	<0.0001
Treatment type				
Deep sedation	46 (90.2)	17 (85)	0	<0.0001
Only AED	5 (9.8)	3 (15)	9 (100)	<0.0001

Data are number (%), mean (SD), or median (IQR).
GCS: Glasgow Coma Scale; APACHE II: The Acute Physiology and Chronic Health Evaluation Score; STESS: Status Epilepticus Severity Score; NeuroICU: neurological intensive care unit; AED: antiepileptic drugs.

Table 3: AEDs administered for management of RSE.

Drug	$n = 80$ No. (%)	Dose used Lowest-highest
Coma induction		
Midazolam	55 (87.3)	0.0006–0.1[‡]
Propofol	28 (44.4)	0.2–12[¶]
Thiopental	3 (4.8)	1–4.5[¶]
AEDs		
Levetiracetam	78 (97.5)	1000–4000[§]
Phenytoin	67 (83.8)	250–500[§]
Topiramate	63 (78.8)	50–1400[§]
Valproate	62 (77.5)	450–3500[§]
Phenobarbital	39 (48.8)	150–500[§]
Other[*]	54 (67.5)	

[*]Carbamazepine, lamotrigine, pregabalin, vigabatrin, and gabapentin.
[‡]mg/kg/hour.
[¶]mg/kg.
[§]mg/day.
AED: antiepileptic drugs; RSE: refractory nonconvulsive status epilepticus.

Table 4: Patient's characteristics according to treatment type.

Characteristics	General anesthesia $n = 63$	AEDs only $n = 17$	P value
Age	43 (19.5)	52 (18.9)	0.1
GCS at NeuroICU admission	9 (7–13)	13 (10–14)	0.003
APACHE II Score	16 (11–21)	8 (4–13)	0.001
STESS 3–6	49 (77.8)	7 (41.2)	0.003
RSE treatment days	5 (5–8)	4 (3–5)	0.001
Average AED used	3.2 (0.8)	2.5 (0.7)	0.003

Data are number (%), mean (SD), or median (IQR).
GCS: Glasgow Coma Scale; APACHE II: The Acute Physiology and Chronic Health Evaluation Score; STESS: Status Epilepticus Severity Score; RSE: refractory status epilepticus; AED: antiepileptic drugs.

embolic stroke with APACHE 23 and the other one with herpes encephalitis who died with propofol syndrome.

At the first month followup, 48.4% of patients had a good functional outcome. The proportion of patients with mRs ≤2 at the same period followup was significantly higher in the non-comatose group, compared to comatose RSE group (66.7% for partial refractory status and 65% for subtle type versus 21.6% in coma RSE, $P < 0.0001$) (Figure 2).

In univariate analysis the factors associated with unfavorable functional outcome included the following: age, stroke, acute neurological lesion, coma, and uncontrolled RSE; whereas underlying epilepsy was associated with good outcome (Table 5).

In multivariate analysis, coma and age ≥60 years were the only factors independently associated with unfavorable short-term functional outcome (Table 8).

4. Discussion

RSE is an underdiagnosed entity, but, with cVEEG monitoring in the NeuroICU, the reports of this disease are increasing [1, 6, 7]. In our center, the incidence of RSE in a 15-month follow-up period was 12.9%.

Patients experiencing RSE can become comatose or have other neurological manifestations such as blinking, sucking, or subtle motor movements in hands, face, or feet [5, 7–11]. The latter group would potentially benefit from cVEEG. In a recent questionnaire directed to neurologists concerning cVEEG use in the management of NCSE, the following factors were considered as the principal indications for its use: previous history of seizures (89%), abnormal eye movements (85%), and altered awareness (69%) [13]. In our cohort,

Table 5: Univariate analysis of factors associated with unfavorable short-term functional outcome.

Factor	OR	95% CI	*P* value
Age >60 years	6	1.6–22.46	0.04
APACHE II Score ≥15	2.81	1.10–7.19	0.028
Etiology: stroke	3.4	1.18–9.77	0.019
Etiology: CNS infection	2.27	0.44–11.77	0.26
Etiology: anoxia/hypoxia	1.55	0.28–8.56	0.47
Etiology: brain tumor	0.37	0.05–2.38	0.27
Etiology: traumatic brain injury	1.9	0.36–10.13	0.36
Systemic abnormalities	1.85	0.18–18.64	0.51
Underlying epileptic disease	0.13	0.03–0.45	0.001
Acute neurological lesion	4.69	1.6–13.78	0.003
Coma	6.9	2.5–19.07	<0.0001
Previous treatment time >10 hours	0.63	0.19–2.01	0.43
Uncontrolled RSE	15.8	1.49–280.5	0.03

OR: Odds ratio; CI: confidence interval; APACHE II: The Acute Physiology and Chronic Health Evaluation Score; CNS: central nervous system; RSE: refractory status epilepticus.

Table 6: Univariate analysis of factors associated with lack of control of RSE.

Factor	Uncontrolled RSE $n = 10$		
	OR	95% CI	*P* value
Age >60 years	0.58	0.11–2.98	0.4
APACHE II Score >15	1.41	0.36–5.46	0.43
Etiology: stroke	5.09	1.2–21.56	0.023
Etiology: neuroinfection	4.57	0.93–22.42	0.08
Etiology: anoxia/hypoxia	0.4	0.03–6.91	0.65
Etiology: brain tumour	1.00	0.14–7.19	0.57
Etiology: traumatic brain injury	0.63	0.07–5.53	0.94
Systemic abnormalities	1.21	0.12–11.43	0.66
Underlying epileptic disease	0.29	0.03–2.44	0.41
Acute neurological lesion	0.83	0.74–0.98	0.11
Coma	0.83	0.21–3.23	0.52
General anesthesia	0.91	0.17–4.77	0.64
Previous treatment time over 10 hours	1.09	0.2–5.68	0.64

APACHE II: The Acute Physiology and Chronic Health Evaluation Score; OR: Odds ratio; CI: confidence interval.

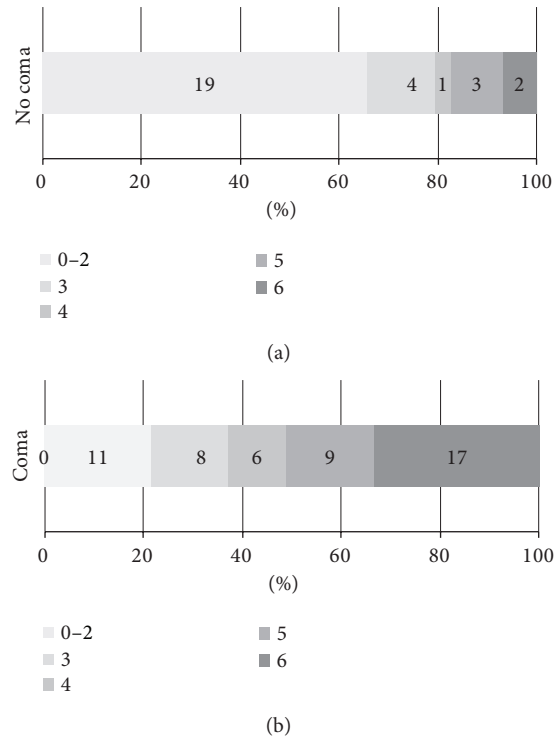

Figure 2: Modified Rankin Scale score in comatose and non-comatose patients.

the most common indications for cVEEG were altered awareness (77.5%), and subtle motor movements (30%).

Around 33–50% of SE cases occur in patients without past medical history of epilepsy and in the context of an acute condition involving the central nervous system, like stroke (20–36%), head trauma (1–26%), metabolic alterations or drug withdrawal (7–26%), central nervous system infections (3–14%), or tumors (5–24%) [1, 2, 4]. In our group, the principal cause of SE was acute neurological lesion (75.1%), with a higher percentage compared to those reported in the literature, with stroke and central nervous system infection being the principal causes. This finding could be explained by the fact that our patients were treated in a NeuroICU.

Our institution is a tertiary referral neurological center, and often times patients' transfer and admission to the NeuroICU with generalized and partial SE are delayed. Therefore, patients with SE who were admitted to our NeuroICU had already received some treatment and met criteria for subclinical or partial NCSE. In fact, most of our patients with RSE were comatose (63.8%), due to the fact that they had experienced severe neurological lesions and greater susceptibility to ictal events [10, 15, 16].

For adequate control of RSE, as we described earlier, the literature suggests two management alternatives: coma induction reaching a burst suppression pattern in the cVEEG and a less aggressive treatment with high-dose AED. Whether one treatment should be chosen over the other has been a subject of debate [15–22]. In recent studies, the STESS showed the power to stratify patients according to SE severity, allowing practitioners to choose the best treatment strategy for each patient [36]. We employed STESS in our cohort, which was one of the tools used to define the treatment. Overall, in patients with low scores, a nonaggressive management was introduced; and in patients with high scores (more than 2 points), deep sedation was used.

For coma induction, medications like barbiturates, propofol, or midazolam are used. A meta-analysis evaluating these three medications in the management of RSE suggested that although pentobarbital seems to be superior to propofol and midazolam in regards to effectiveness of RSE control (to stop seizures and to avoid their relapse), this drug is associated with more hypotensive episodes, demanding vasopressor use [15]. Considering this evidence and due to comparable mortality between these medications, our group employs more frequently midazolam followed by propofol,

Table 7: Outcome of RSE according to level of consciousness.

Outcome	Coma $n = 51$	Noncoma $n = 29$	P value
Treatment days	5 (4–8)	5 (3.5–6)	0.057
Mechanical ventilation days	12 (8–18)	8 (4.7–13)	0.03
Tracheostomy	40 (78.4)	8 (27.6)	<0.0001
Gastrostomy	15 (29.4)	3 (10.3)	0.05
Infectious complications (VAP, UTI, BSI)	21 (41.2)	13 (44.8)	0.75
Vasopressor use	24 (47.1)	9 (31)	0.16
NeuroICU days	14 (10–22)	8 (3–12.5)	<0.0001
RSE Control	45 (88.2)	25 (86.2)	0.52
In-hospital mortality	16 (31.4)	2 (6.9)	0.012
Unfavorable mRs at 1 month	40 (78.8)	10 (34.5)	<0.0001

Data are number (%), mean (SD), or median (IQR).
VAP: ventilator associated pneumonia, UTI: urinary tract infection; BSI: blood stream infection; NeuroICU: neurological intensive care unit; RSE: refractory status epilepticus; mRs: modified Rankin scale.

Table 8: Prognostic factors for unfavorable short-term functional outcome in multivariate analysis.

	Factor	OR	95% CI	P value
Nonfavorable mRs (≥3)	Coma	8.84	2.62–29.84	<0.0001
	Age >60 years	6.36	1.44–28	0.014

leaving barbiturates only in patients with head trauma associated with refractory high intracranial pressure, where the barbiturate could be used for both purposes.

According to the literature, coma-inducing medications titrated to attain EEG burst suppression pattern were associated with a significant lower incidence of breakthrough seizures [15]. This suggests that the burst suppression pattern associated with pharmacological sedation is produced by the effect over the GABA receptors of the cortical-thalamus pathways, generating a cortical synchronization that could explain the control of ictal activity. This argument explains our reason to induce burst suppression pattern in most of our patients (78.8%): 90% comatose RSE and 85% subclinical RSE.

In the last few years, several reports have been published concerning the use of new AEDs for control of RSE, such as levetiracetam and topiramate, which have demonstrated favorable results in these patients [37–43]. Our management algorithm also included the use of these drugs. In fact, levetiracetam and topiramate were the most-commonly used new-generation AED (97.5% and 77.5%) in our patients.

The management of patients with RSE requires a multidisciplinary team, and continuous hemodynamic monitoring is needed to minimize possible complications associated to the medical management. In our patients, hypotension was the most common medical complication (about 33% of the cases) which is similar to the published literature [15, 17, 21, 22].

The other important component of the neuromonitoring of patients with RSE is cVEEG which is noninvasive and enables assessment of cerebral function and multimodal monitoring in the neuroICU [12–14]. The literature suggests that 4–48% of the comatose critically ill patients may have nonconvulsiveictal activity. Therefore, cVEEG monitoring is indispensable for detection and management of these episodes [9–11]. cVEEG monitoring has been useful in the classification of comatose RSE, based upon EEG patterns. Lateralized Epileptiform Discharge (LED) coma is the result of focal lesions leading to focal or lateralized discharges; conversely, Generalized Epileptiform Discharge (GED) coma is the consequence of diffuse central nervous system discharges due to infections, intoxications, or occupying space lesions that produce intracranial hypertension, like tumors [11]. In our cohort, 58.8% of patients had a GED-coma RSE pattern.

It is important to emphasize that despite having new AEDs and cVEEG, RSE progression is generally time dependent, and it is imperative to avoid delays in its management. In addition, new evidence has shown that it is possible to achieve functional and cognitive recovery after prolonged SE [44, 45]. In this cohort RSE was successfully controlled within 3 days in 87.5% of patients; this is consistent with data reported in different series, and possibly the time to achieve control is determined by the underlying etiology of severe neurological injury.

Our review of the literature showed that mortality from RSE can reach 50%; in this study, in-hospital mortality was 22.5% at one-month followup; about half of the patients regained their independent daily activities, with a higher proportion in the non-comatose group. This fact supports recent findings about aggressive management of these patients to obtain an acceptable recovery [44, 45].

Overall, RSE is associated with high morbidity and mortality, and the reported risk factors of poor prognosis are the following: elderly, mechanical ventilation necessity, coma, hypoxic ischemic encephalopathy lesions, and associated comorbidities [15–18]. Our multivariate analysis showed that

coma and age over 60 years were the only predictors independently associated with unfavorable short-term functional outcome. These may indicate that these variables should be considered in future studies for the management of patients with RSE [44, 45].

Our study has several limitations. Our analysis was retrospective and as such is subject to bias. In addition, the reported cohort stems from a single center, and the results may not be applicable to all patients with RSE. Furthermore, our sample size is relatively small and our results may have to be replicated prospectively and in a larger sample population. Lastly, we do not have data on long-term clinical outcomes including quality of life. The latter should be included in future studies.

In summary, our study includes patients with RSE managed by a multidisciplinary team following a defined management protocol. Our data suggest that patients with RSE can improve, even though comatose patients may have a grimmer prognosis. More publications and randomized-controlled trials are required to clarify the best management and monitoring for patients with RSE.

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