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Original article

ANTIEPILEPTIC AND ANESTHETIC DRUGS IN THE INTENSIVE CARE UNIT. THEIR IMPACT ON NON-CONVULSIVE STATUS EPILEPTICUS MORTALITY

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Abstract

Background: Status epilepticus (SE) is a neurological emergency. Non-convulsive status epilepticus (NCSE) can only be diagnosed by electroencephalogram (EEG) because the motor clinical symptoms are usually subtle or absent, with high mortality. The best treatment is still unknown.

Objectives: Our aim was to assess anticonvulsive and anesthetic drugs in NCSE and their correlation with Epidemiology-based Mortality Score in Status Epilepticus (EMSE), Status Epilepticus Severity Score (STESS) and mortality.

Methods: Retrospective, observational, descriptive, cross-sectional study. Ninety patients in intensive care unit over 18 years-old (57 females [63.3%] and 33 males [36.6%], mean age 63.5 years [SD ± 19]) with NCSE, at the Buenos Aires British Hospital. Data was collected between January 2018 and June 2021. An adjusted multivariate statistical analysis was performed. Ninety-five (95%) CI, $p<0.05$ as statistically significant. EMSE and STESS were used in this study.

Results: Total mortality rate was 37.8% (34/90), and in patients ≥ 65 years-old (54/90) it was 40.7% (22/54). Patients with 0-2 STESS (11/90) were discharged, while those with STESS ≥ 3 (79/90) had a 43% death rate (34/79). Patients with EMSE < 34 (27/90) had 7.4% (2/27) death rate, while those with EMSE ≥ 34 (63/90) had 50.8% (32/63). No significant differences were found in survival with regard to the number of antiepileptic drugs administered. Patients treated with anesthetics presented a 2.6-fold death risk increase (95% CI 1.001-6.83).

Discussion: It could be assumed that mortality rate increases 2.6-fold when patients are treated with anesthetic drugs, regardless of the number of antiepileptic drugs previously administered.

Key words: non convulsive status epilepticus, antiepileptic drugs, anesthetic drugs

Resumen

Drogas antiepilépticas y anestésicas en la unidad de terapia intensiva. Su impacto en la mortalidad en el estado de mal epiléptico no convulsivo

Introducción: El estado de mal epiléptico (SE) es una emergencia neurológica. El SE no convulsivo (SENC) se diagnostica únicamente por electroencefalograma debido a la ausencia o sutileza de sintomatología clínica motora, con una mortalidad elevada. No se conoce aún el mejor tratamiento.

Objetivos: Evaluar drogas anticonvulsivas y anestésicas en el SENC y su correlación con *Epidemiology-based Mortality Score in Status Epilepticus (EMSE)*, *Status Epilepticus Severity Score* (STESS) y el índice de mortalidad.

Métodos: Estudio retrospectivo, observacional, descriptivo, de corte transversal. Noventa pacientes ≥ 18 años (57 mujeres [63.3%] y 33 hombres [36.6%], media de edad 63.5 años [DS ± 19]) con diagnóstico de SENC, en

el Hospital Británico. Estudio realizado entre enero 2018 y junio 2021. Análisis estadístico multivariado ajustado. IC 95% p< 0.05 como estadísticamente significativo. Se utilizaron escalas de EMSE y STESS.

Resultados: La mortalidad total fue de 37.8% (34/90). Los pacientes ≥ 65 años (54/90) presentaron una mayor tasa de muerte 40.7% (22/54), todos aquellos con STESS de 0-2 (11/90) egresaron, mientras que entre los que presentaron ≥ 3 (79/90) el 43% (34/79) falleció. De los pacientes con EMSE < 34 (27/90) dos fallecieron (7.4%) y de aquellos con EMSE ≥ 34 (63/90) falleció el 50.8% (32/63). No hallamos diferencias significativas entre cantidad de drogas antiepilépticas utilizadas y supervivencia. Pacientes con anestésicos tuvieron un aumento del riesgo de muerte 2.6 veces (IC 95% 1.001-6.83).

Discusión: De acuerdo a esto la mortalidad con drogas anestésicas aumenta, independientemente de la cantidad de drogas anticonvulsivas utilizadas previamente.

Palabras clave: estado de mal epiléptico no convulsivo, drogas antiepilépticas, drogas anestésicas

KEY POINTS

- There was no evidence correlating a greater number of administered antiepileptic drugs and higher mortality rates. Patients who were administered anesthetic drugs died after 21 days, whereas those who were not, died after 60 days. These results presume the high mortality rate associated with anesthetic drugs, regardless of the number of anticonvulsant drugs previously administered.

Current knowledge

- One third of patients are refractory to benzodiazepines and treatment at next stage is still being discussed. There is no Class I evidence to favor one drug over another.
- When SE becomes Refractory and Super-Refractory, controversy surrounding the treatment is even greater and intravenous anesthetic drugs have been recommended.

Contribution of the article to current knowledge

- With these results could be presume the high mortality rate can be associate with anesthetic drugs, regardless of the number of anticonvulsant drugs previously administered.

Status epilepticus (SE) is a neurological emergency with an estimated incidence of 60 cases per 100 000 per year and a 20% mortality rate around the world.

"SE health-care cost in refractory stages is high[1], and a German study has estimated a cost of €1.365 a day"[2].

The concept "Time is brain" applies to SE, which has been reported to worsen when it is prolonged. Early and appropriate treatment is associated with lower morbidity and mortality rates and a lower number of administered drugs. This results in a shorter hospital stays and lower health-care costs.

SE represents approximately 3.5% of ICU (intensive care unit) patients and 15% of neurology department inpatients[3].

In Argentina, its adjusted annual incidence was 24.3 cases per 100 000 per year, in 2013[3].

Non-Convulsive Status Epilepticus (NCSE) has a 10% global incidence in patients with impaired awareness and a 16% incidence on elderly patients upon admission[4]. Patients with a history of epilepsy, elderly or septic patients are at higher risk of developing NCSE.

It has been demonstrated that NCSE patients' condition is more likely to deteriorate when the episode durations prolonged or due to systemic complications. However, etiology is the most influential factor to develop NCSE.

The ILAE (*International League Against Epilepsy*) defines SE as "a condition resulting either from the failure of the mechanisms responsible for seizure termination or from the initiation of mechanisms which lead to abnormally prolonged seizures (after time point t1). It is a condition that can have long-term consequences (after time point t2), including neuronal death, neuronal injury, and alteration of neuronal networks, depending on the type and duration of seizures"[5].

Time point t1 determines the time when the seizure is considered to be abnormally prolonged and when the treatment should be started. Time point t2 determines the time beyond which ictal activity is considered to be a risk and determines how aggressive the treatment should be.

Some types of SE can only be diagnosed by EEG monitoring because motor clinical symptoms are usually absent or very subtle; sometimes the only symptom is the impaired awareness.

Therefore, differentiating SE with predominantly motor symptoms (Convulsive SE) and SE without symptoms (Non-Convulsive SE) it been proposed[7, 8].

Ictal patterns shown in the EEG are not specific, and they have limited clinical value in convulsive SE due to overloading movement and muscle artifice. However, EEG monitoring is essential to diagnose NCSE because clinical signs may be very subtle or even nonexistent.

As it was mentioned above, NCSE diagnosis sometimes is not straight forward, so it is essential to perform an EEG. Hence, in 2013, the Salzburg criteria were proposed to diagnose NCSE. These criteria have a 97.7% sensitivity, 89.6% specificity. Therefore, the diagnosis is 92.5% accurate[7-9].

The ILAE describes a staged treatment[10, 11]. Initially it must be with benzodiazepines. Several studies have demonstrated benzodiazepines efficacy and safety. Up to two thirds of cases are successfully controlled in this early stage. Midazolam efficacy is 73.4% while lorazepam efficacy is 63.4%[12].

Around 30-40% of patients go into Stage II: Established SE (refractory to benzodiazepines). Treatment in Stage II is still being discussed. Administration of antiepileptic drugs (AEDs) like phenytoin (PHT), valproic acid (VPA), levetiracetam (LEV), phenobarbital (PB) or lacosamide (LCM) is recommended. There is no Class I evidence to favor one drug over another. The efficacy of these drugs to control SE has been tested in cohort and case and control trial studies for years[13, 14]. VPA has been proved to have an efficacy rate of 70-76%; PB, 73-80% (although with a high rate of respiratory depression); LEV, 50-70%; PHT, 50-58% (with several cardiovascular secondary effects and respiratory depression); LCM, 56%[15-21]. Currently, perampanel (PER) or brivaracetam (BVT) are being studied in order to prove their efficacy to control seizures. So far there is little reliable literature[22-25].

As to stages III and IV, when SE becomes Refractory (RSE) and Super-Refractory (SRSE), controversy surrounding the treatment is even greater[26]. For years, and even today, intravenous anesthetic drugs (IVADs) like propofol, midazolam, thiopental or pentobarbital had been recommended.

Several studies had shown that using IVADs is associated with higher infection rates (11% vs. 43%), a 2.9-fold death risk increase, a high rate of cardiovascular complications and severe immunosuppression[27-31].

In order to assess SE outcome and mortality rate, two scores had been proposed[32]. EMSE (Epidemiology-based Mortality Score in Status Epilepticus, cutoff value of ≥ 34) and STESS (Status Epilepticus Severity Score, cutoff value of ≥ 3) can predict short-term mortality with high sensitivity and specificity. The worst outcomes were associated with the following factors: old age (≥ 65), New Onset Refractory Status Epilepticus (NORSE), NCSE, the impaired consciousness at the onset of the episode, the duration of the seizures, comorbidities, etiology, EEG features, infections, respiratory failure, or cardiovascular failure[15, 30-38].

NCSE has a high morbidity-mortality rate because it does not present evident motor clinical signs. Sometimes the diagnosis, and therefore, appropriate treatment, can be delay.

In the last few years, several studies had shown that certain drugs are more effective than others to treat NCSE. Also, some drugs can have potential secondary effects that increase mortality rates.

We proposed to study NCSE management, establishing the therapy provided in our healthcare center and the patients evolution, comparing with the available literature.

The main objective is to assess the use of antiepileptic and anesthetic drugs in relation to NCSE mortality rate in the ICU.

A secondary objective is to assess the correlation between the pharmacological treatment in NCSE patients in the ICU and how they had responded. This was observed in the clinical signs and symptoms and in the EEG. The values of STESS and EMSE were correlated with the patients' clinical and EEG evolution.

We presumed that mortality rate of NCSE patients in the ICU correlates with the chosen therapy.

Material and methods

Study design

An observational, descriptive, cross-sectional study was performed. Data was collected and analyzed from the time of admission to the time of discharge or decease.

The reviewed data was collected from the Buenos Aires British Hospital clinical records and neurology department database from January 2018 to June 2021.

STESS and EMSE scores were applied to determine mortality risk.

The primary research question was to establish the mortality rate correlating to the scores values and the administered drugs.

Participants

Ninety (90) patients over 18 years-old, diagnosed with NCSE and fulfilling Salzburg criteria were included. Patients with post-anoxic encephalopathy (NCSE after cardiac-respiratory arrest) and/or insufficient data were excluded.

Variables

The variables included were sex, age, history of epilepsy, comorbidities, level of consciousness upon admission, worst type of epileptic seizures, etiology, EEG pattern (at onset and after treatment), antiepileptic drugs administered (loading and maintenance dose) and outcome (hospital discharge or decease). The Apache II score was applied to avoid potential confounders and bias sources.

Statistical Analysis

Basic descriptive statistics were used and the confidence interval was estimated at 95%, with a value of $p < 0.05$ as statistically significant. An age-adjusted, univariate and multivariate analysis was performed. The cutoff values stablished were ESME ≥ 34 points, STESS ≥ 4 points and Apache-II ≥ 31. STATA 17 statistical software was used. X^2 test was performed with the dichotomous data. All patients with missing data were excluded from the study.

Results

We enrolled 97 patients with SE at the Buenos Aires British Hospital from January 1st 2018 to June 30th 2021. Seven (7) patients were excluded because of the following causes: a 16-year-old patient; 4 patients with Convulsive SE (1 with myoclonic status and 3 with focal status due to a space-occupying lesion); one patient diagnosed with NCSE but still hospitalized at the end of trial; a patient with missing data, thus hindering assessment of pharmacological treatment and its results (Fig. 1).

Demographic data, clinical features and pharmacological comparisons can be observed in Table 1.

Figura 1 | Flowchart: Patients enrolled. Patients excluded and grounds for their exclusion

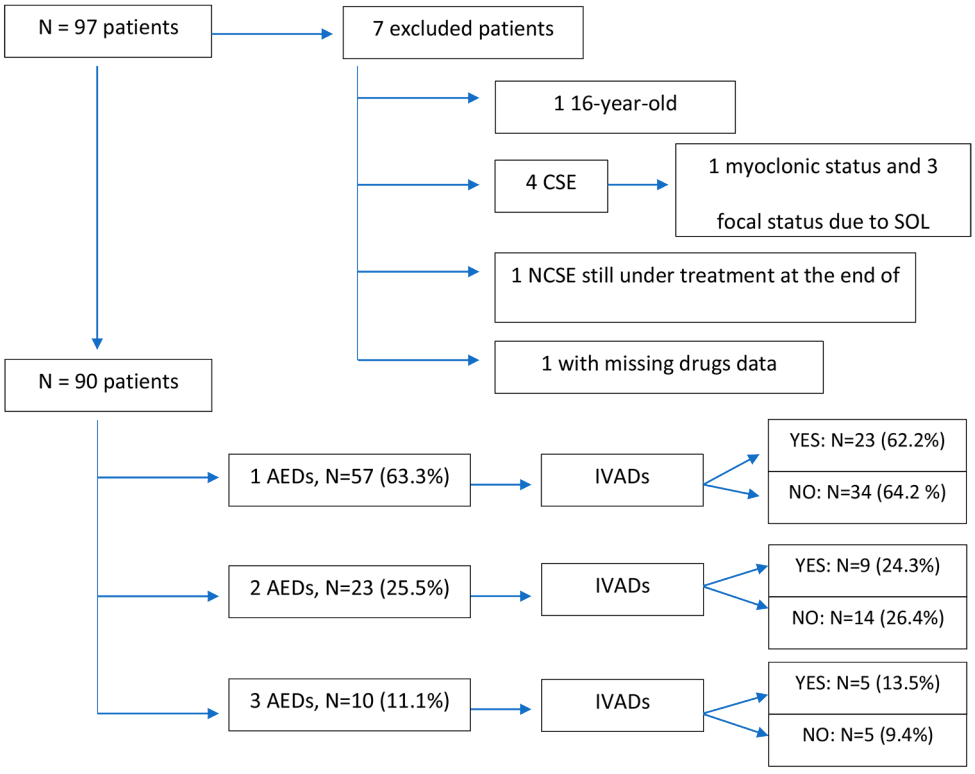


Tabla 1 | Demographic and clinical features of patients with and without continuous IV anesthetic drugs treatment

	Total cohort (n = 90)	Patients without IVADs (n = 53)	Patients with IVADs (n = 37)	p value
Demographics				
Sex, n (%)				
Female	57 (63.3)	40 (75.5)	17 (45.9)	0.0072
Male	33 (36.6)	13 (24.5)	20 (54.1)	
Age, y, mean ± SD	63.5 ± 19	65.7 ± 18.2	59.0 ± 20.1	0.18
Etiology, n (%)				
Criptogenic	13 (14.4)	7 (13.2)	6 (16.2)	0.76
Reduction or Discontinuation of AEDs	5 (5.6)	4 (7.6)	1 (2.7)	0.64
Hyponatremia	6 (6.7)	5 (9.4)	1 (2.7)	0.39
Metabolic	3 (3.3)	2 (3.8)	1 (2.7)	1.00
Systemic Infection	14 (15.6)	9 (17)	5 (13.5)	0.77
CNS infections	7 (7.8)	2 (3.8)	4 (10.8)	0.22
Metabolic + Infectious	12 (13.3)	5 (9.4)	7 (19)	0.22
Uremic/Hepatic Encephalopathy	3 (3.3)	2 (3.8)	1 (2.7)	1.00
SOL	8 (8.9)	7 (13.2)	1 (2.7)	0.13
Acute/Remote Stroke	8 (8.9)	4 (7.6)	4 (10.8)	0.71
Drugs/Alcohol	1 (1.1)	0 (0)	1 (2.7)	0.41
Multifactorial	10 (11.1)	5 (9.4)	5 (13.5)	0.73
Pre-existing antiepileptic treatment, n (%)	21 (23.3)	16 (30.2)	5 (13.5)	0.08
SE treatment. Number of AEDs (excluding IVADs), n (%)				
1 AEDs	57 (63.3)	34 (64.2)	23 (62.2)	1.00
2 AEDs	23 (25.5)	14 (26.4)	9 (24.3)	1.00
3 AEDs	10 (11.1)	5 (9.4)	5 (13.5)	0.73
IVADs during SE, n (%)				
Midazolam only	–	–	7 (18.9)	0.0014
Propofol only	–	–	12 (32.4)	< 0.00001
Midazolam and Propofol	–	–	18 (48.7)	< 0.00001
Midazolam and Barbiturates	–	–	0 (0)	1.00
STESS Characteristics				
Awake or Somnolent, n (%)	67 (74.5)	45 (85)	22 (59.5)	
Stuporous or Comatose, n (%)	23 (25.5)	8 (15)	15 (40.5)	0.013
Worst Seizure Type - All were NCSE				
Age≥65, y, n (%)	53 (54)	37 (70)	16 (45)	0.016
No history of seizures, n (%)	69 (76.7)	38 (71.7)	31 (83.8)	0.2
STESS, Median (ICC 25-75%)	4 (3-5)	5 (3-5)	4 (3-5)	0.4
EMSE, Median (ICC 25-75%)	41 (30-62)	38.5 (26.2-57.5)	52.5 (36-78.2)	0.013

CNS: central nervous system; SOL: space-occupying lesion; SE: status epilepticus; AEDs: antiepileptic drugs; IVADs: intravenous anesthetic drugs; STESS: Status Epilepticus Severity Score; EMSE: Epidemiology-based Mortality score in Status Epilepticus; NCSE: non convulsive status epilepticus

A univariate and multivariate statistical analysis was performed on a total of 90 subjects. Fifty-seven (57) were females (63.3%). The mean age was 63.5 years-old (SD ± 19). Thirty-seven-point eight percent (37.8%) of patients died during hospital stay (34/90).

Seventy-nine (79) out of 90 patients were reported with generalized NCSE (13.3% after a convulsive SE evolved [12/90]), with a 34.4% death rate (31/79).

As to STESS values, 12.2% of the 90 patients (11/90) had a score between 0-2 and all were dis-

charged; 41.1% (37/90) had a score between 3-4, where 16 died (43.2%); 46.7% (42/90) had a score between 5-6, where 17 died (40.5%).

As to EMSE values, 27 of the 90 patients (30%) had a score of < 34 and a 7.4% death rate (2/27), while 63 of patients (70%) with a score ≥ 34 had a 50.8% death rate (32/63).

Out of the 90 patients, 37 (41.1%) were administered anesthetic drugs. Twenty-nine (29) of them (78.4%) had an EMSE value of ≥ 34, out of which 20 (69%) died at the hospital. Seventy-nine of the total sample (87.8%) had a STESS value of ≥ 3, out of which 34 (43%) died.

Out of the 90 patients, 53 were not administered anesthetic drugs (58.9%). Thirty-four of them (64.2%) had an EMSE value of ≥ 34, out of which 12 (35.3%) died at the hospital. Forty-five of them (84.9%) had a STESS value of ≥ 3, out of which 13 (28.9%) died.

It is worth highlighting the finding that patients who were administered anesthetic drugs were younger (< 65 years-old). This data was statistically significant (p 0.016).

No significant differences were found between EMSE (Fig. 2) and STESS (Fig. 3) values correlating to the number of administered AEDs.

Treatment and outcome: use of antiepileptic drugs and anesthetics

No significant differences were found on survival rates correlating to the number antiepileptic drugs: 1 drug, OR 1.255, 95% CI 0.42-3.75; 2 drugs, OR 0.669, 95% CI 0.2-2.2; 3 drugs, OR 1.38, 95% CI 0.23-8.3 (Fig. 4). This suggests that using 3 anticonvulsant drugs does not increase death risk.

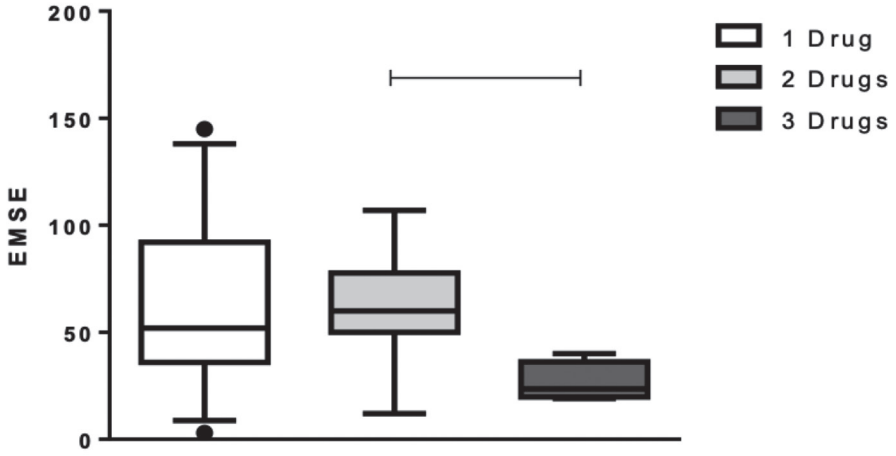
Fifty-three out of 90 (58.9%) of patients were not administered anesthetic drugs and 24.5% of them died (13/53). Among patients who were administered anesthetic drugs (37/90 [41.1%]), 56.8% died (21/37).

Upon performing a multivariate analysis, patients who were administered anesthetic drugs died after 21 days, while those who were not, died after 60 days (Fig. 5). It could be presumed that using anesthetic drugs carries a 2.61-fold death rate increase (95% CI 1.001-6.83). Even thought, more studies must be performed to confirm this association. The analyzed data would not be enough to confirm this hypothesis.

Discussion

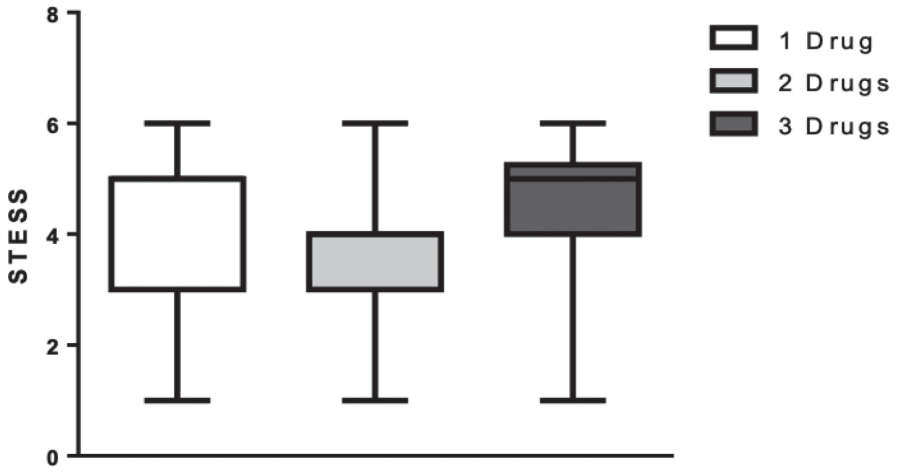
SE is known to have a high morbidity-mortality rate globally. For years, benzodiazepines have been known to be the most effective treatment for Early SE (Stage I). However, there is insufficient Class I evidence to favor one drug over another for Established SE (Stage II) treatment. In our health-care center, the main antiepileptic drug used was levetiracetam, probably due to the lack of available endovenous drugs in our hospital. Phenytoin it is rarely used due to its

Figura 2 | Epidemiology-based Mortality Score in Status Epilepticus and number of antiepileptic drugs administered. No statistically significant differences were found



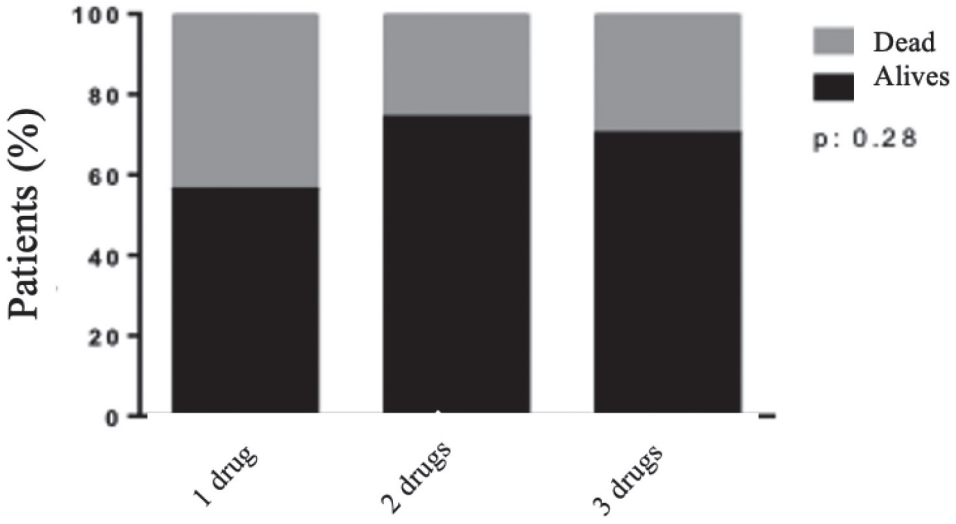
EMSE: Epidemiology-based Mortality score in Status Epilepticus

Figura 3 | Status Epilepticus Severity Score and number of antiepileptic drugs administered. No statistically significant differences were found



STESS: Status Epilepticus Severity Score

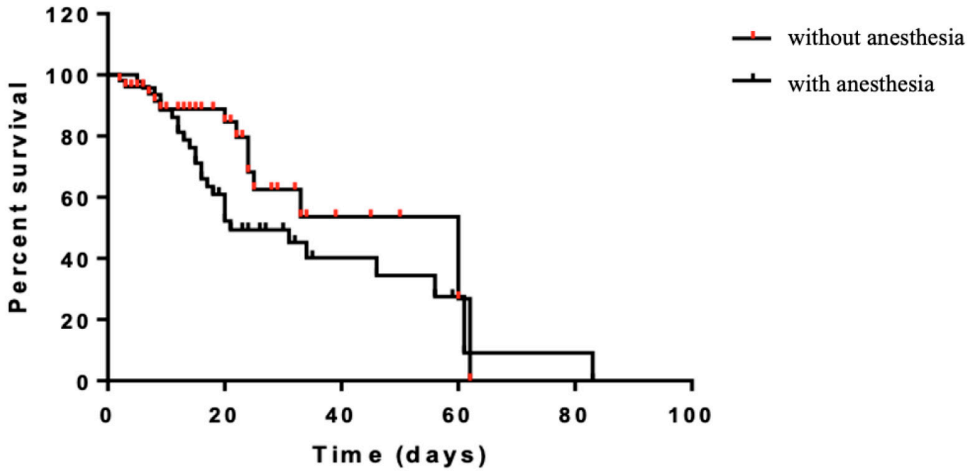
Figura 4 | Correlation between number of administered antiepileptic drugs and survival. No significant differences were found on survival rates correlating to the number anticonvulsant drugs regardless of age and Status Epilepticus Severity Score or Epidemiology-based Mortality score in Status Epilepticus values. Using 3 anticonvulsant drugs does not increase death risk



associated high cardiologic secondary effects rate, high toxicity and narrow therapeutic window.

Some literature reports a 3-fold death rate increase with the use of anesthetic drugs in Refractory and Super-Refractory SE[39]. It had been reported an increase of infections, longer ICU stays and greater vasoactive drugs requirement rates. Despite this data, ICUs continue using anesthetic drugs[40]. We had observed a 56.8% (21/37) death rate in patients who were administered anesthetic drugs and a 24.5% (13/53) death rate in patients who were not. We presumed anesthetic drugs could cause a 2.6-fold death rate increase. Death rate was lower (30% [3/10]) in patients who were administered 3 anticonvulsant drugs (10/90), compared to those who were administered anesthetic drugs (37/90-41.1%) (mor-

Figura 5 | Mortality curve comparing patients with or without IV anesthetic drugs



Mean survival: 60 days without anesthesia; 21 days with anesthesia. Without anesthesia: Ratio 2.857, 95% CI 1.47-5.53. With anesthesia: Ratio 0.35, 95% CI 0.18-0.68

tality rate 21/37-56.8%). Mortality was an independent and statistically significant variable.

It is also worth highlighting that death rate was higher (50.8% [32/63]) among patients with ESME ≥ 34 compared to those with a lower score (7.4% [2/27]).

As to STESS, some papers use a cutoff value of ≥ 3 and others a cutoff value of ≥ 4. In this study, a higher mortality rate was observed with a cutoff value of ≥ 3. With STESS 0-2, a 0% mortality rate was observed. With STESS ≥ 3, the patients had a 43% (34/79) mortality rate.

Due to the scarcity of literature on mortality rates associated with anesthetic drugs use in NCSE management, the number of subjects required for this kind of study to be significant has not been defined. Therefore, we cannot assess whether the number of subjects meets the requirement. Further studies with a greater number of subjects are warranted to conduct a better analysis.

There was no evidence correlating a greater number of administered antiepileptic drugs and higher mortality rates. Patients who were administered anesthetic drugs died after 21 days, whereas those who were not, died after 60 days. These results shown the high mortality rate associated with anesthetic drugs, regardless of the number of antiepileptic drugs previously administered.

Furthermore, it has been established that it is important to use EMSE and STESS scores to predict mortality with a cutoff value of ≥ 34 and ≥ 3, respectively. Other important predictive factors are the EEG pattern after treatment, the patients' age and their history of epilepsy.

Further studies similar to ours, with a greater number of subjects, may revolutionize and modify the proposed and chosen therapy for NCSE in Refractory and Super-Refractory Stages, thus modifying patients' survival rates.

Study limitations: The management protocol in the ICU was unclear. The choice between antiepileptic and/or anesthetic drugs was not predetermined or reported. Furthermore, many patients were not administered benzodiazepines as a first line treatment.

Patients with equal EMSE, STESS and Apache II values were treated with either more than one antiepileptic drug or with anesthetic drugs, without following a management protocol. This presume that the clinical condition of patients does not modify their survival.

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Conflict of interest: None to declare

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