Epilepsy & Behavior 140 (2023) 109093

Contents lists available at ScienceDirect

Epilepsy & Behavior

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

Treatment of benzodiazepine-refractory status epilepticus: A retrospective, cohort study

Eleonora Rollo [a], Marina Romozzi [a], Fedele Dono [b,c,*], Daniela Bernardo [d], Stefano Consoli [b], Francesca Anzellotti [b], Leopoldo Ricciardi [e], Luisassunta Paci [e], Stefano L. Sensi [b,c], Giacomo Della Marca [a,f], Serenella Servidei [a,g], Paolo Calabresi [a,f], Catello Vollono [a,g]

[a] Dipartimento Universitario di Neuroscienze, Università Cattolica del Sacro Cuore, Rome, Italy
[b] Dipartimento di Neuroscienze, Imaging e Scienze Cliniche, "G. D'Annunzio" Università di Chieti-Pescara, Chieti, Italy
[c] Behavioral Neurology and Molecular Neurology Units, Center for Advanced Studies and Technology-CAST-, University G. D'Annunzio of Chieti-Pescara, Italy
[d] Centro Clinico NEMO, Fondazione Policlinico Universitario Agostino Gemelli IRCCS, Rome, Italy
[e] Clinica Neurologica, Ospedale "F. Renzetti" Lanciano, Italy
[f] Neurologia, Dipartimento di Scienze dell'invecchiamento, Neurologiche, Ortopediche e della Testa-Collo, Fondazione Policlinico Universitario Agostino Gemelli IRCCS, Rome, Italy
[g] Neurofisiopatologia, Dipartimento di Scienze dell'invecchiamento, Neurologiche, Ortopediche e della Testa-Collo, Fondazione Policlinico Universitario Agostino Gemelli IRCCS, Rome, Italy

ARTICLE INFO

Article history:
Received 27 June 2022
Revised 10 January 2023
Accepted 11 January 2023
Available online 3 February 2023

Keywords:
Status epilepticus
Refractory SE
SE treatment
Intensive care
Antiseizure medication

ABSTRACT

Introduction: Status epilepticus (SE) is a frequent neurological emergency, derived from the failure of mechanisms responsible for seizure termination. The present study aims to compare the efficacy of the most common antiseizure medications (ASMs) employed for the treatment of benzodiazepine-refractory SE.
Methods: We performed a retrospective cohort study of all SE episodes treated in our hospital between January 2016 and December 2020. Inclusion criteria were: age $\geq$ 18 years; a diagnosis of status epilepticus. Exclusion criteria were: status epilepticus resolved by initial therapy with benzodiazepines; impossibility to retrieve medical records. We considered as effective the ASM that was the last drug introduced or increased in dose before termination of SE and without changes in the co-medication.
Results: A total of 244 episodes in 219 patients were included in the study. The mean age of the final study cohort was 63.6 ± 19.2, with 108 (49%) men. In the total cohort, phenytoin (PHT) showed the highest response rate (57.6%), followed by lacosamide (LCM) (40.7%) and valproate (VPA) (39.8%). The comparative efficacy among the different drugs was significantly different ($p < 0.001$). In the pairwise comparisons, VPA was superior to levetiracetam (LEV) (response rate: 39.75% vs 24.71%; $p = 0.004$), but not to LCM. Phenytoin had a significantly higher resolution rate compared to VPA (response rate: 57.63% vs 39.75%; $p = 0.02$) and LEV (response rate: 57.63% vs 24.71; $p < 0.001$). The clinical predictors of anaesthetics administration were a disorder of consciousness upon clinical presentation, previous diagnosis of epilepsy, and younger age.
Conclusion: In our cohort of SE, PHT showed higher effectiveness in terminating established SE, as well as refractory SE in the subgroup of patients treated with anaesthetics.

1. Introduction

Status epilepticus (SE) is a condition resulting from the failure of the mechanisms involved in seizure termination or the initiation of mechanisms responsible for seizure prolongation [1]. Status epilepticus represents a common neurologic emergency, with a pooled annual incidence rate of approximately 12.6 per 100,000 person-years [2]. It requires timely treatment to reduce morbidity and mortality, which approximates 15% in adults [2]. Therefore, an urgent treatment escalation approach is employed, with different drugs used in early (stage I), established (stage II), refractory (stage III), and super-refractory SE (stage IV) [3]. While nearly two-thirds of episodes of early SE are controlled by intravenous benzodiazepines, approximately 40% of generalized convulsive SE are refractory to benzodiazepine treatment [4]. This condition, referred to as established SE, is commonly treated with intra-

* Corresponding author at: Dipartimento di Neuroscienze, Imaging e Scienze Cliniche, "G. D'Annunzio" Università di Chieti-Pescara, Chieti, Italy.
E-mail address: fedele.dono@unich.it (F. Dono).

https://doi.org/10.1016/j.yebeh.2023.109093
1525-5050/

venous antiseizure medications (ASMs): valproate (VPA), levetiracetam (LEV), phenytoin/fosphenytoin (PHT), phenobarbital (PB), and lacosamide (LCM). However, to date, there is no class I evidence for choosing one drug over another [3]. In 2019 the Established Status Epilepticus Treatment Trial (ESETT), a multicenter, randomized, blinded, a comparative-effectiveness trial of LEV, PHT, and VPA for the treatment of convulsive benzodiazepine-refractory SE, revealed that the three drugs did not differ significantly with regard to effectiveness and safety [5]. A recent randomized clinical trial showed that LCM and VPA had comparable efficacy and safety in the treatment of established SE [6]. A meta-analysis supported the use of VPA, LEV, and PB as first-line therapy in benzodiazepine-resistant convulsive status epilepticus [7], even though uncertainties remain about whether these drugs are equally effective [8]. Moreover, the existing data on LCM in comparison with other ASMs are scarce to provide recommendations [9]. The present retrospective study aimed to compare the efficacy of the most common ASMs employed in clinical practice for the treatment of benzodiazepine-refractory SE.

2. Methods

The present study is a single-centre, retrospective, observational, cohort study. We retrospectively reviewed the medical records of patients with SE hospitalized in the Fondazione Policlinico Universitario Agostino Gemelli, IRCCS, in Rome between January 2016 and December 2020. Three neurologists (ER, DB, and FD), trained in epilepsy, identified patients with SE by searching the electronic archive of medical records. Inclusion criteria were: age $\geq$ 18 years; a diagnosis of status epilepticus. Exclusion criteria were: status epilepticus resolved by initial therapy with benzodiazepines; impossibility to retrieve medical records.

According to the administration of anaesthetics during the treatment of SE, patients were divided into two subgroups: patients treated with anaesthetics (Anaesth+) and patients not treated with anaesthetics (Anaesth–).

The study was performed in agreement with the Helsinki declaration and was approved by the ethics committees of the Catholic University of Rome.

2.1. Status epilepticus

Status epilepticus was defined according to the 2015 International League Against Epilepsy (ILAE) definition [1]. A diagnosis of established SE (i.e. benzodiazepine-refractory SE) was formulated when seizures persisted or recurred after the initial administration of adequate doses of benzodiazepines. The minimal adequate cumulative doses of benzodiazepines were defined as diazepam at a dose of 10 mg, lorazepam at a dose of 4 mg, or midazolam at a dose of 10 mg [10]. Patients treated with an inadequate dose of benzodiazepine were not included in the study. A diagnosis of refractory status epilepticus (RSE) was formulated when seizures persisted despite adequate treatment with second-line drugs. Anaesthetic drugs were employed for the treatment of RSE, according to current clinical practice guidelines [10] by means of infusion of sedative drugs, such as propofol, midazolam, or ketamine.

Status epilepticus was diagnosed clinically, and electroencephalography (EEG) confirmation was required to establish a diagnosis of nonconvulsive episodes, according to our clinical practice [11]. For each status epilepticus, we evaluated semiology, aetiology, and treatment. According to semiology, SE was classified as generalized convulsive, focal motor, focal non-convulsive, generalized non-convulsive and unknown [1]. Based on aetiology, status epilepticus was classified as symptomatic (acute, remote, progressive, due to ASM non-compliance or rapid withdrawal), and unknown [1]. The ASMs used in each status epilepticus were recorded. We considered as effective the ASM that was the last drug introduced or increased in dose before SE resolution and without changes in the comedication [12]. Electroencephalographic confirmation of SE termination was achieved in all cases by means of EEG monitoring or EEG control performed within 24 hours. The severity of each SE was assessed by means of the Status Epilepticus Severity Score (STESS), including the following variables: severe consciousness impairment, convulsive seizure, lack of previous seizures, and higher age [13].

2.2. Clinical information

The following data were recorded: demographic information (age, sex); a previous definite diagnosis of epilepsy; epilepsy aetiology, defined according to the 2017 ILAE classification of the epilepsies [14]; Glasgow Coma Scale (GCS) score upon first medical evaluation; laboratory analysis including pH, creatine kinase (CK), presence of cerebrospinal fluid (CSF) abnormalities. For each SE, the complications arising after the onset of SE and occurring during hospitalization were collected.

2.3. Endpoints

The primary endpoint was the comparative ASM efficacy (among VPA, LEV, PHT, and LCM). Secondary endpoints were: ASMs response rates in the subgroup of patients not treated with anaesthetics (Anaesth–); ASMs response rates in the subgroup of patients treated with anaesthetics (Anaesth+); clinical predictors of anaesthetics administration.

2.4. Statistical analysis

Numerical variables are presented as mean ± standard deviation, and as median and interquartile range; categorical variables are presented as number (n) and percentage. The variables analysed are listed in Table 1. Taking into consideration the mean response rate for second-line ASMs [7], and assuming a power of the study of 0.95, and alpha = 0.01, we calculated a minimum sample size of 56 cases of SE to achieve the primary endpoint.

The ASMs' comparative efficacy was tested by means of a Chi-square test. In order to avoid family-wise type I errors, a formal Bonferroni correction was applied to each family of comparisons, by dividing the limit of significance by the number of comparisons (i.e., total cohort, subgroup Anaesth+, subgroup Anaesth–). Therefore, the threshold for significance was set at p = 0.05/3 = 0.017. A post-hoc analysis was performed to assess the head-to-head comparison of efficacy between the different ASMs.

As a secondary analysis, patients were divided into two subgroups based on anaesthetics administration: patients treated with anaesthetics (Anaesth+) and patients not treated with anaesthetics (Anaesth–). After testing all variables for normal distribution, by means of the Shapiro–Wilk test, univariate analysis was performed. All study variables were compared between the subgroups Anaesth+ and Anaesth–. To compare numerical variables, we used a nonparametric test (Mann–Whitney U- test); for categorical variables, we adopted Pearson's chi-square (χ^2).

Variables compared in the univariate analysis were entered into a multivariate logistic regression analysis to determine adjusted odds ratios (ORs). Multivariate analysis was performed to adjust the effect for potential confounders. The model for multivariate analysis was made by choosing variables for the significance in the univariate comparison and clinical relevance [15]. The Hosmer–Lemeshow test and Nagelkerke R2 were used to evaluate the goodness of fit for the logistic regression model. All statistics

Table 1
Demographic and clinical characteristics of the study cohort. Abbreviations: Anaesth+, patients treated with anaesthetics; Anaesth–, patients not treated with anaesthetics; SE, status epilepticus; NCSE, non-convulsive status epilepticus; ASM, anti-seizure medication; STESS, Status Epilepticus Severity Score; GCS, Glasgow Coma Scale; CK, creatine kinase; CSF, cerebrospinal fluid; SD, standard deviation; IQR, interquartile range.

	Total (n = 244)	Anaesth + (n = 114)	Anaesth – (n = 130)	Mann-Whitney U Test	Pearson's Chi-Square	
Sex (male) n(%)	108 (49%)	57 (57%)	51(42.8%)		3.87	p = 0.05
Age mean (SD)	63.64(19.15)	59.63(16.70)	67 (20.45)	5502.5		p = 0.001
Epilepsy History n (%)	92 (42%)	34 (34%)	58 (48.74)		3.12	p = 0.077
Epilepsy aetiology						
Structural n(%)	65 (70.7%)	23(67.6%)	42 (72.4%)		8.73	p = 0.120
Infectious n(%)	3 (3.3%)	0 (0%)	3 (5.1%)			
Immune n(%)	1 (1%)	0 (0%)	1 (1.7%)			
Genetic n(%)	4 (4.3%)	1 (3%)	3 (5.1%)			
Unknown n(%)	19 (20.7%)	10 (29.4%)	9 (15.5%)			
SE semeiology						
Generalized Convulsive n (%)	107 (43.9%)	65 (57%)	42 (32.3%)		27.34	
Focal motor n (%)	73 (29.9%)	20 (17.5%)	53 (40.8%)			
Focal NCSE n (%)	28 (11.5%)	8 (7%)	20 (15.4%)			p < 0.001
Generalized NCSE n(%)	33 (13.5%)	18 (15.8%)	15 (11.5%)			
Unknown n(%)	3 (1.2%)	3 (2.6%)	0 (0%)			
SE aetiology						
Acute n(%)	132 (54.1%)	66 (57.9%)	66 (50.8%)		4.37	p = 0.358
Remote n(%)	24 (9.8%)	7 (6.1%)	17 (13.1%)			
Progressive n(%)	22 (9%)	11 (9.6%)	11 (8.5%)			
ASMs non compliance n(%)	41 (16.8%)	17 (14.9%)	24 (18.5%)			
Unknown n(%)	25 (10.2%)	13 (11.4%)	12 (9.2%)			
Number of ASMs mean (SD)	2,70 (1.20)	2,78 (1.22)	2,63 (1.17)	7933.5		p = 0.322
Exitus n(%)	55 (22.5%)	35 (30.7%)	20 (14.5%)		8.24	p = 0.016
Complications n(%)	103 (42.2%)	64 (56.1%)	39 (30%)		17.01	p < 0.001
STESS median (IQR)	3 (2–4)	3 (2–5)	3 (2–4)	7480.5		p = 0.124
GCS median (IQR)	8 (3–12)	3 (3–8)	10 (5–13)	2462.0		p < 0.001
CK mean (SD)	630.89 (1448.54)	793.58 (1407.74)	475.76 (1486.18)	1052.5		p = 0.126
pH mean(SD)	7.409 (0.081)	7.41 (0.08)	7.41 (0.08)	1204.5		p = 0.919
CSF						
Altered n(%)	22 (9%)	16 (14%)	6 (4,6%)		0.17	p = 0.684
Normal n(%)	36 (14.8%)	23 (20.2%)	13 (10%)			

were performed using Statistical Package for Social Science (SPSS®) software version 22 (SPSS, Inc.).

3. Results

During the study period, 385 episodes of status epilepticus were identified. After reviewing for inclusion and exclusion criteria, a total of 244 episodes in 219 patients were included in the study. The study flowchart, with detailed reasons for exclusion, is described in Fig. 1. The mean age of the final study cohort was 63.6 ± 19.2 years, with 108 (49%) men. Ninety-two (42%) patients had a previous definite diagnosis of epilepsy. The most common aetiology of the SE episodes was acute symptomatic (54.1%), followed by ASMs non-compliance (16.8%). Among the causes of SE, acute or previous brain ischemia, as well as haemorrhage, was present in 25.4% of cases, meningoencephalitis in 12.3%, brain tumours in 12.3%, metabolic derangements in 9.8%, autoimmune encephalitis in 7.3%, hypoxic encephalopathy in 3.3%; aetiology was unknown in 10.2% of cases. According to semiology, SE episodes were classified into 107 generalized convulsive (43.9%), 73 focal motor (29.9%), 28 focal non-convulsive (11.5%), 33 generalized non-convulsive (13.5%), and 3 unknown onsets (7.4%). SE episodes were resolved after a mean of 2.7 ± 1.2 ASMs. Complications were encountered in 103 (43.2%) episodes, and the mortality rate was 22.5%. CSF analysis was performed only in 58 cases, showing abnormalities in 22. The recurrence of SE was observed in 22 patients. In such patients, SE recurred up to six times during the same hospitalization or in subsequent hospitalization periods. The demographic and clinical characteristics of the study cohort are displayed in Table 1.

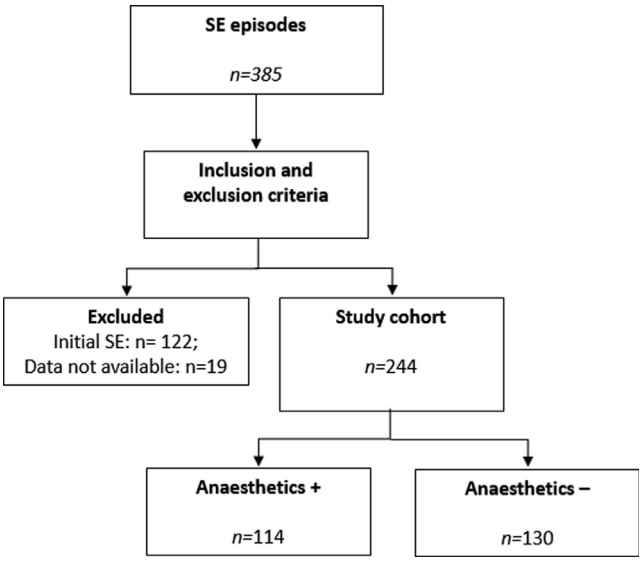

Fig. 1. Study flowchart, depicting the enrolment process.

3.1. Treatment choices and ASM comparative efficacy

Among the different ASMs, LEV and VPA were the most prescribed medications, as they were administered in 170 and 161 episodes respectively. PHT and LCM were less frequently employed, accounting for 59, and 27 cases (Table 2). Other drugs that were administered were PB, carbamazepine, brivaracetam, topiramate, and perampanel. These drugs were not considered for statistical comparison due to the low number of cases. Anaesthetics were employed in 114 episodes of RSE. The most frequently employed anaesthetic was propofol, followed by midazolam, keta-

Table 2
Antiseizure medications' comparative efficacy in the total cohort, and the subgroups Anaesth+ and Anaesth–. Abbreviations: Anaesth+, patients treated with anaesthetics; Anaesth–, patients not treated with anaesthetics.

	Effective administration/total administrations (n/n)	Response Rate (%)	Chi Square-test	
Total cohort				
Valproic acid	64/161	39.75	22.57	**p < 0.0001***
Levetiracetam	42/170	24.71		
Phenytoin	34/59	57.63		
Lacosamide	11/27	40.74		
Anaesth +				
Valproic acid	22/83	26.51	19.39	**p < 0.001***
Levetiracetam	11/78	14.1		
Phenytoin	20/38	52.63		
Lacosamide	2/7	28.57		
Anaesth –				
Valproic acid	42/78	53.85	11.15	p = 0.025
Levetiracetam	31/92	33.7		
Phenytoin	14/21	66.67		
Lacosamide	9/20	45		

mine, and remifentanil. Notably, in our cohort there were only five super-refractory SE; they were not analysed as a specific subgroup due to the low number of cases.

The response rates of the single ASMs are reported in Table 2. In the total cohort, PHT showed the highest response rate (57.6%), followed by LCM (40.7%) and VPA (39.8%). The overall comparative efficacy among the different drugs was significantly different (Chi-Square Test: 22.57, p < 0.001). In the pairwise comparisons, VPA was superior to LEV (VPA response rate: 39.75% vs LEV response rate: 24.71%, Chi-Square Test: 7.92, p = 0.004), but not to LCM (VPA response rate: 39.75 vs LCS response rate: 40.74, Chi-Square Test: 0.01, p = 0.09). PHT had a significantly higher resolution rate compared to VPA (PHT response rate: 57.63 vs VPA response rate: 39.75, Chi-Square Test: 4.88, p = 0.02) and to LEV (PHT response rate: 57.63 vs LEV response rate: 24.71, Chi-Square Test: 19.95, p = 0.00001). In the total cohort, no other significant difference was observed in the head-to-head comparisons (Table 3).

As a secondary analysis, we compared ASMs efficacy in the subgroup Anaesth+. Also in this subgroup, PHT showed the highest response rate (52.6%). The different response rates are detailed in Table 2. In the pairwise comparisons, PHT was superior to VPA (PHT response rate: 52.63 vs VPA response rate: 26.51, Chi-Square Test: 6.74, p = 0.009) and LEV (PHT response rate: 52.63 vs LEV response rate: 14.10, Chi-Square Test: 17.45, p = 0.00001). Moreover, VPA showed a higher response rate compared to LEV (VPA response rate: 26.51 vs LEV response rate: 14.10, Chi-Square Test: 3.07, p = 0.07) (Table 3).

For what concerns the subgroup Anaesth–, the difference between the ASMs' response rates was not statistically significant. However, PHT showed a trend towards superiority (Table 2).

Table 3
Pairwise comparisons of the different ASMs in the total cohort, and the subgroups Anaesth+ and Anaesth–. Abbreviations: Anaesth+, patients treated with anaesthetics; Anaesth–, patients not treated with anaesthetics; VPA, valproic acid; LEV, levetiracetam; LCM, lacosamide; PHT, phenytoin; n.p., not performed.

	Response Rate comparison (%)	Chi Square-test	p-value
Total Cohort			
VPA vs LEV	39.75 vs 24.71	7.92	**p = 0.0049***
PHT vs VPA	57.63 vs 39.75	4.88	**p = 0.0271***
VPA vs LCM	39.75 vs 40.74	0.01	p = 0.90
PHT vs LEV	57.63 vs 24.71	19.95	**p < 0.00001***
LEV vs LCM	24.71 vs 40.74	2.29	p = 0.1306
PHT vs LCM	57.63 vs 40.74	1.49	p = 0.2215
Anaesth +			
VPA vs LEV	26.51 vs 14.1	3.07	0.0796
VPA vs PHT	26.51 vs 52.63	6.74	**0.0094***
VPA vs LCM	26.51 vs 28.57	0.11	0.7442
LCM vs LEV	28.57 vs 14.1	0.22	0.6378
LEV vs PHT	14.1 vs 52.63	17.45	**<0.00001***
PHT vs LCM	52.63 vs 28.57	0.58	0.448
Anaesth –			
VPA vs LEV	53.85 vs 33.7	n.p.	n.p.
VPA vs PHT	53.85 vs 66.67	n.p.	n.p.
VPA vs LCM	53.85 vs 45	n.p.	n.p.
LCM vs PHT	45 vs 66.67	n.p.	n.p.
PHT vs LEV	66.67 vs 33.7	n.p.	n.p.
LCM vs LEV	45 vs 33.7	n.p.	n.p.

3.2. Clinical comparison between subgroups

In the univariate comparison between the subgroups Anaesth+ and Anaesth–, patients treated with anaesthetics were younger (Anaesth+:58.6 ± 17.6 vs Anaesth– 65.9 ± 20.3; U-test = 5502.5, p = 0.001), had lower GCS upon first medical examination (Anaesth+:3 (3–8) vs Anaesth–: 10 (5–13); U-test = 2462.0, p < 0.001), experienced higher rates of complications (Anaesth +:64/114 vs Anaesth– 39/130; χ^2 = 17.01, p < 0.001) and higher in-hospital mortality (Anaesth+:35/114 vs Anaesth– 20/130; χ^2 = 8.24, p = 0.016). When compared to the Anaesth– group, patients in the Anaesth+ group presented differences in SE semiology (Table 1). The post-hoc analysis showed a higher administration of anaesthetics in the generalized convulsive SE episodes compared to focal motor SE (generalized convulsive: 57% vs focal motor: 17,5%; χ^2 = 18.05; p < 0.001), and focal NCSE (generalized convulsive: 57% vs focal NCSE: 7%; χ^2 = 8.00; p < 0.005), but not compared to generalized NCSE (generalized convulsive: 57% vs generalized NCSE: 15,8%; χ^2 = 1.81; p = 0.178), nor unknown onset SE (generalized convulsive: 57% vs unknown onset: 2,6%; χ^2 = 0.60; p = 0.437). Focal motor SE was significantly associated with anaesthetics administration compared to unknown onset SE (focal motor: 17,5% vs unknown onset: 2,6%; χ^2 = 4.17; p = 0.041). Focal motor SE was significantly superior in the group without anaesthetics administration compared to Generalized NCSE (focal motor: 40,8% vs generalized NCSE: 15%; χ^2 = 6.15;

p = 0.013). No other significant differences were observed between the two subgroups. For detailed efficacy measures see Table 1.

In the multivariate analysis, clinical predictors of anaesthetics administration were low GCS upon clinical presentation (OR = 0.798; CI: 0.725–0.878; p < 0.001), epilepsy history (OR = 0.438; CI: 0.193–0.994; p = 0.048), and younger age (OR = 0.957; CI: 0.935–0.980; p < 0.001) (Fig. 2). The total number of ASMs (OR = 0.907; CI: 0.680–1.209; p = 0.50) and STESS (OR = 1.05; CI: 0.764–1.445; p = 0.763) did not reach statistical significance.

4. Discussion

The present study aimed to retrospectively analyse the real-world treatment of benzodiazepine-refractory status epilepticus in a large cohort of patients admitted to our hospital over 5 years. For the detection of SE resolution, we considered the last drug (i.e., ASMs or anaesthetics) administered before the SE termination. Indeed, this is one of the most effective criteria, as shown by previous literature [12].

To date, no high-quality, evidence-based data are available to suggest the superiority of one ASM over another in the treatment of benzodiazepine-refractory SE. Data emerging from the literature suggest that the efficacy of ASMs gradually decreases with each subsequent administration, resulting that the efficacy of the first drug administered being higher than the second, which is, in turn, higher than the third [17]. It is, therefore, of paramount importance to have a recommendation on which drug to choose first in the setting of an established status epilepticus.

In our cohort, phenytoin showed to be superior in terminating SE as compared to the other ASMs commonly employed. Such superiority was confirmed also in patients with refractory status epilepticus undergoing anaesthetic treatment. Phenytoin was

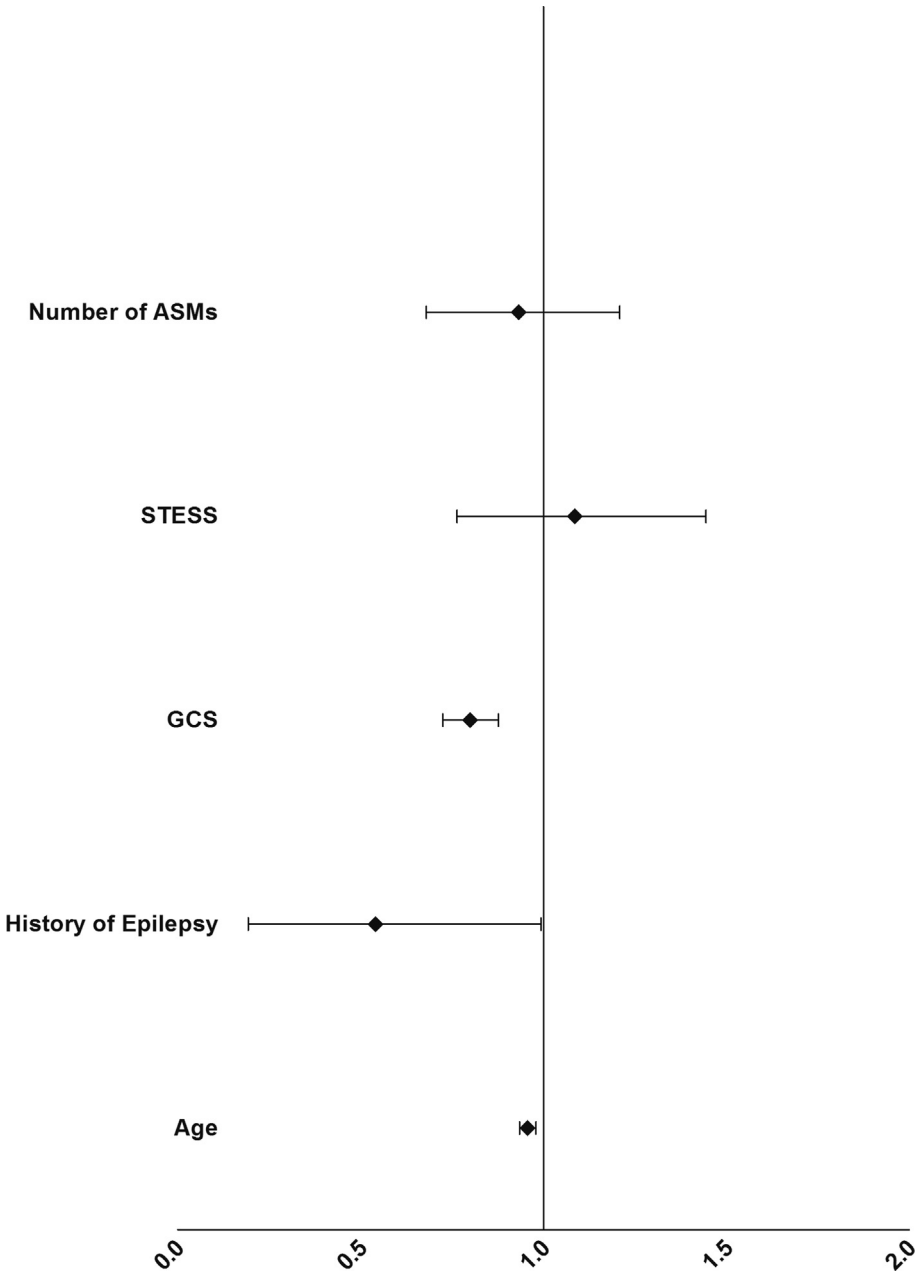

Fig. 2. Clinical predictors of anaesthetics administrations.

effective in more than half of the episodes in which it was employed. The response rate was in line with a recent meta-analysis in which phenytoin showed a pooled mean efficacy of 50.2% [7]. In addition, these results partially agreed with those shown in a recent randomized double-blind controlled trial (ESETT trial) in which levetiracetam, valproate, and phenytoin led to seizures cessation in almost half of the episodes of benzodiazepine-refractory SE, although revealing no significant difference in effectiveness among the three drugs [5]. However, a previous retrospective study comparing LEV, PHT, and VPA as second-line agents in 198 SE episodes, showed that the treatment success rate of VPA was higher as compared to PHT and LEV in the univariate analysis, even if only the difference between VPA and LEV persisted after adjustment for confounders [18]. In addition, a further meta-analysis [16] and several randomized trials [19,20] supported the notion that there was no superiority of PHT compared to VPA, LEV, or PB in terms of seizure cessation in benzodiazepine-refractory SE [16].

Hence, some discrepancies are evident between our results and those shown in the previous studies. To discuss these differences, it must be pointed out that generally, all the meta-analyses conducted on the treatment of the benzodiazepine-refractory SE [19,20] included very heterogeneous studies, especially in terms of study design as well as SE definition, SE aetiology, semiology, and patient's age. On the other hand, the currently available randomized control trials on the treatment of benzodiazepine-refractory SE generally took into consideration generalized tonic-clonic SE and anyone except one [5] were focused on the adult population. Thus, the patient's age (which is much older in our cohort compared to previous studies), the SE semiology (which includes several SE semiology and not just generalized tonic-clonic SE), and the stratification of ASMs response rates according to concomitant anaesthetics administration are some features which undoubtedly contributed to the novelty of our findings.

The frequency of choice of PHT in our cohort was inferior to that of VPA and LEV, reflecting a certain resistance to its employment in real-world practice, maybe due to the worries of possible severe side effects (e.g., cardiac arrhythmia, hypotension, thrombosis and inflammation at the injection site). Notably, in our cohort use of phenytoin was not associated with complications, nor with mortality in a univariate analysis. It is worth clarifying that in our cohort phenytoin was employed as a sodic phenytoin formulation for intravenous administration, and that the dosing regimen was established according to the current clinical practice guidelines (15–18 mg/kg, with infusion rate up to 50 mg/min)[10]. Moreover, the rates of complications and mortality did not differ significantly among the different ASMs (Table 4).

As a secondary outcome, we analyzed the predictors of anaesthetics administration. Patients with younger age, a definite previous diagnosis of epilepsy, and a disorder of consciousness upon first clinical presentation had a higher probability to undergo sedation and intensive care treatment. The younger age as a predictor for anaesthetics administration may, at least partially, be explained by the higher propensity to intubate and provide intensive treatment in a younger patient. The clinical predictors of anaesthetics administration have not been systematically assessed in literature, rather the predictors of RSE have been explored. A previous study found younger age as a predictor of RSE, even if such association was not confirmed in a multivariate analysis [21]. The presence of a disorder of consciousness upon the first presentation is an established predictor of RSE in literature [22,23], increasing nearly five times the odds of developing an RSE, as reported in a previous study [21].

In our study, patients treated with anaesthetics had a worse prognosis, as expressed by higher mortality and higher rates of complications. In our cohort, the in-hospital mortality was 22.5%, which is in line with previously reported mortality in SE [24]. Such high mortality may be explained by the relatively old population in our cohort (i.e., mean age higher than 60 years), which in turn reflects the high prevalence of stroke and brain tumours among SE causes.

The main limitation of our study is the retrospective design, based on chart reviews. Even if, in the study protocol, a common criterion was applied to consider SE cessation (i.e., the last drug administered before seizure cessation), the actual termination of SE was assessed by the treating clinicians, not in a homogenous manner. Anyway, an electroencephalographic control on the first day and/or monitoring was performed in all the cases. Even if this may represent a bias in the ASMs efficacy assessment, the large number of SE episodes included in our study may help to limit such bias. Another limitation of the real-world setting is that it is not possible to adjust for time to treatment[25] and to exclude a potential residual therapeutic effect of the previously introduced ASM, in the cases where a sequence of multiple drugs was employed.

The strengths of our study are the large sample size of our cohort and, despite its limits, the real-world setting which allows for rendering a picture of the clinical management of this neurological emergency in a tertiary reference academic hospital. Indeed, randomized clinical trials are often heterogeneous and strict in terms of inclusion criteria, efficacy measure, outcome assessment, and type of SE enrolled, and do not reflect the real-life circumstances which are encountered in daily clinical practice.

5. Conclusion

Overall, data emerging from our large cohort of SE suggest the effectiveness of PHT in terminating established SE, as well as refractory SE Anaesth+. Moreover, PHT was not associated with complications or increased mortality in our cohort. The superiority of PHT emerging from our results adds knowledge to the real-world management of SE, which may provide a clinical practice recommendation to guide the physician on the choice of the first drug for the treatment of benzodiazepine-refractory SE. Even with the limitations of a retrospective, not-blinded study, we believe that PHT is a good treatment option that may prevent the administration of anaesthetics, and furthermore manages to stop refractory SE under treatment with anaesthetics in more than half of employed cases. Taking into account that the ASM effectiveness and the prevention of anaesthetic treatment are the major predictors of a better outcome in a patient with SE, we advise considering

Table 4
Rates of complications and mortality with the different anti-seizure medications. ASM, antiseizure medication; VPA, valproic acid; LEV, levetiracetam; LCM, lacosamide; PHT, phenytoin.

ASM	Complications/n of administrations n (%)	p-value	Death/n of administrations n(%)	p-value
VPA	70/161 (43.5%)	p = 0.953	46/160 (28.7%)	p = 0.424
LEV	80/170 (47.1%)		41/170 (24.1%)	
PHT	28/59 (47.5%)		13/59 (22%)	
LCM	14/27 (51.8%)		3/27 (11.1%)	

treatment with phenytoin at least at the same rate as the other ASMs.

Data Availability

The data that support the findings of this study are available from the corresponding author upon reasonable request.

Competing Interests

The authors declare no funding.

Ethical publication statement

Authors confirm to have read the Journal's position on issues involved in ethical publication and affirm that this report is consistent with those guidelines.

Author Contribution

E.R., M.R., and C.V. contributed to the conception and design of the study. F.D., D.B., S.C., F.A., L.R., L.P., applied eligibility criteria for inclusion in the study. C.V. and G.D.M. performed the statistical analysis. E.R., M.R., F.D. and C.V. wrote the manuscript and supervised all the data. All authors contributed to manuscript revisions, read and approved the submitted version.

Data Availability

The data that support the findings of this study are available from the corresponding author upon reasonable request.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

References

[1] Trinka E, Cock H, Hesdorffer D, Rossetti AO, Scheffer IE, Shinnar S, et al. A definition and classification of status epilepticus – Report of the ILAE Task Force on Classification of Status Epilepticus. Epilepsia 2015;56(10):1515–23. https://doi.org/10.1111/epi.13121.

[2] Lv RJ, Wang Q, Cui T, Zhu F, Shao XQ. Status epilepticus-related etiology, incidence and mortality: A meta-analysis. Epilepsy Res 2017;136:12–7. https://doi.org/10.1016/j.eplepsyres.2017.07.006.

[3] Trinka E, Kälviäinen R. 25 years of advances in the definition, classification and treatment of status epilepticus. Seizure - Eur J Epilepsy 2017;44:65–73. https://doi.org/10.1016/j.seizure.2016.11.001.

[4] Silbergleit R, Durkalski V, Lowenstein D, Conwit R, Pancioli A, Palesch Y, et al. Intramuscular versus intravenous therapy for prehospital status epilepticus. N Engl J Med 2012;366(7):591–600. https://doi.org/10.1056/NEJMoa1107494.

[5] Kapur J, Elm J, Chamberlain JM, Barsan W, Cloyd J, Lowenstein D, et al. Randomized Trial of Three Anticonvulsant Medications for Status Epilepticus. N Engl J Med 2019;381(22):2103–13. https://doi.org/10.1056/NEJMoa1905795.

[6] Misra UK, Dubey D, Kalita J. Comparison of lacosamide versus sodium valproate in status epilepticus: A pilot study. Epilepsy Behav 2017;76:110–3. https://doi.org/10.1016/j.yebeh.2017.07.005.

[7] Yasiry Z, Shorvon SD. The relative effectiveness of five antiepileptic drugs in treatment of benzodiazepine-resistant convulsive status epilepticus: a meta-analysis of published studies. Seizure 2014;23(3):167–74. https://doi.org/10.1016/j.seizure.2013.12.007.

[8] Vossler DG, Bainbridge JL, Boggs JG, Novotny EJ, Loddenkemper T, Faught E, et al. Treatment of Refractory Convulsive Status Epilepticus: A Comprehensive Review by the American Epilepsy Society Treatments Committee. Epilepsy Curr 2020;20(5):245–64. https://doi.org/10.1177/1535759720928269.

[9] Fernández IS, Gaínza-Lein M, Lamb N, Loddenkemper T. Meta-analysis and cost-effectiveness of second-line antiepileptic drugs for status epilepticus. Neurology 2019;92(20):e2339–48. https://doi.org/10.1212/WNL.0000000000007503.

[10] Minicucci F, Ferlisi M, Brigo F, Mecarelli O, Meletti S, Aguglia U, et al. Management of status epilepticus in adults. Position paper of the Italian League against Epilepsy. Epilepsy Behav 2020;102:. https://doi.org/10.1016/j.yebeh.2019.106675106675.

[11] Beniczky S, Hirsch LJ, Kaplan PW, Pressler R, Bauer G, Aurlien H, et al. Unified EEG terminology and criteria for nonconvulsive status epilepticus. Epilepsia 2013;54(s6):28–9. https://doi.org/10.1111/epi.12270.

[12] Redecker J, Wittstock M, Benecke R, Rösche J. Comparison of the effectiveness of four antiepileptic drugs in the treatment of status epilepticus according to four different efficacy criteria. Epilepsy Behav 2015;49:351–3. https://doi.org/10.1016/j.yebeh.2015.04.038.

[13] 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(10):1561–6. https://doi.org/10.1007/s00415-008-0989-1.

[14] Scheffer IE, Berkovic S, Capovilla G, Connolly MB, French J, Guilhoto L, et al. ILAE classification of the epilepsies: Position paper of the ILAE Commission for Classification and Terminology. Epilepsia 2017;58(4):512–21. https://doi.org/10.1111/epi.13709.

[15] Bursac Z, Gauss CH, Williams DK, Hosmer DW. Purposeful selection of variables in logistic regression. Source Code Biol Med 2008;3:17. https://doi.org/10.1186/1751-0473-3-17.

[16] Hoshiyama E, Kumasawa J, Uchida M, Hifumi T, Moriya T, Ajimi Y, et al. Phenytoin versus other antiepileptic drugs as treatments for status epilepticus in adults: a systematic review and meta-analysis. Acute Med Surg 2022;9(1):e717. https://doi.org/10.1002/ams2.717.

[17] Glauser T, Shinnar S, Gloss D, Alldredge B, Arya R, Bainbridge J, et al. Evidence-Based Guideline: Treatment of Convulsive Status Epilepticus in Children and Adults: Report of the Guideline Committee of the American Epilepsy Society. Epilepsy Curr 2016;16(1):48–61. https://doi.org/10.5698/1535-7597-16.1.48.

[18] Alvarez V, Januel JM, Burnand B, Rossetti AO. Second-line status epilepticus treatment: Comparison of phenytoin, valproate, and levetiracetam. Epilepsia 2011;52(7):1292–6. https://doi.org/10.1111/j.1528-1167.2011.03056.x.

[19] Dalziel SR, Borland ML, Furyk J, Bonisch M, Neutze J, Donath S, et al. Levetiracetam versus phenytoin for second-line treatment of convulsive status epilepticus in children (ConSEPT): an open-label, multicentre, randomised controlled trial. Lancet 2019;393(10186):2135–45. https://doi.org/10.1016/S0140-6736(19)30722-6.

[20] Lyttle MD, Rainford NEA, Gamble C, Messahel S, Humphreys A, Hickey H, et al. Levetiracetam versus phenytoin for second-line treatment of paediatric convulsive status epilepticus (EcLiPSE): a multicentre, open-label, randomised trial. Lancet 2019;393(10186):2125–34. https://doi.org/10.1016/S0140-6736(19)30724-X.

[21] Sutter R, Kaplan PW, Marsch S, Hammel EM, Rüegg S, Ziai WC. Early predictors of refractory status epilepticus: an international two-center study. Eur J Neurol 2015;22(1):79–85. https://doi.org/10.1111/ene.12531.

[22] Agan K, Afsar N, Midi I, Us O, Aktan S, Aykut-Bingol C. Predictors of refractoriness in a Turkish status epilepticus data bank. Epilepsy Behav 2009;14(4):651–4. https://doi.org/10.1016/j.yebeh.2009.02.008.

[23] Novy J, Logroscino G, Rossetti AO. Refractory status epilepticus: a prospective observational study. Epilepsia 2010;51(2):251–6. https://doi.org/10.1111/j.1528-1167.2009.02323.x.

[24] Opic P, Sutter R. The Unease When Using Anesthetics for Treatment-Refractory Status Epilepticus: Still Far Too Many Questions. J Clin Neurophysiol 2020;37(5):399–405. https://doi.org/10.1097/WNP.0000000000000606.

[25] Hill CE, Parikh AO, Ellis C, Myers JS, Litt B. Timing is everything: Where status epilepticus treatment fails. Ann Neurol 2017;82(2):155–65. https://doi.org/10.1002/ana.24986.