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RESEARCH ARTICLE

Phenobarbital in super-refractory status epilepticus (PIRATE): A retrospective, multicenter analysis

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Abstract

Objective: Super-refractory status epilepticus (SRSE) is an enduring or recurring SE after 24 h or more of general anesthesia. This study aimed to evaluate the efficacy and safety of phenobarbital (PB) for the treatment of SRSE.

Methods: This retrospective, multicenter study included neurointensive care unit (NICU) patients with SRSE treated with PB between September 2015 and September 2020 from six participating centers of the Initiative of German NeuroIntensive Trial Engagement (IGNITE) to evaluate the efficacy and safety of PB treatment for SRSE. The primary outcome measure was seizure termination. In addition, we evaluated maximum reached serum levels, treatment duration, and clinical complications using a multivariate generalized linear model.

Results: Ninety-one patients were included (45.1% female). Seizure termination was achieved in 54 patients (59.3%). Increasing serum levels of PB were associated with successful seizure control (per μg/mL: adjusted odds ratio [adj.OR] = 1.1, 95% confidence interval [CI] 1.0–1.2, $p < .01$). The median length of treatment in the NICU was 33.7 [23.2–56.6] days across groups. Clinical complications occurred in 89% ($n = 81$) of patients and included ICU-acquired infections, hypotension requiring catecholamine therapy, and anaphylactic shock. There was no association between clinical complications and treatment outcome or in-hospital mortality. The overall average modified Rankin scale (mRS) at discharge from the NICU was 5 ± 1. Six patients (6.6%) reached mRS ≤ 3, of whom five were successfully treated with PB. In-hospital mortality was significantly higher in patients in whom seizure control could not be achieved.

Significance: We observed a high rate in attainment of seizure control in patients treated with PB. Success of treatment correlated with higher dosing and serum levels. However, as one would expect in a cohort of critically ill patients with prolonged NICU treatment, the rate of favorable clinical outcome at discharge from the NICU remained extremely low. Further prospective studies

evaluating long-term clinical outcome of PB treatment as well as an earlier use of PB at higher doses would be of value.

KEYWORDS

phenobarbital, SRSE, super-refractory status epilepticus

1 | INTRODUCTION

Status epilepticus (SE) is a life-threatening neurologic emergency and is defined as a prolonged epileptic seizure of more than 5 min for tonic–clonic SE and 10 min for all other seizure types.[1]

SE that cannot be terminated with the use of first- and second-line antiepileptic drugs (AEDs) is considered refractory status epilepticus (RSE). RSE is managed through the administration of general anesthesia, aiming for burst suppression on electroencephalography (EEG). An enduring or recurring SE after 24 h or more of general anesthesia is defined as super-refractory status epilepticus (SRSE). Approximately 15% of all SE becomes super-refractory and the occurrence of SRSE is associated with poor functional outcome and an overall mortality of 30%–50%.[2–6] Thus SRSE is a rare and heterogeneous disease with limited data to rely on for its management, making it difficult to further explore treatment options in prospective, randomized trials. Despite a large array of available therapeutic substances, there are no substantial data to guide the choice, dosage, or duration of any given treatment, since all conducted studies so far rely on small retrospective series or single case reports.[7]

In their guidelines for the treatment of convulsive SE the American Epilepsy Society describes phenobarbital (PB) as an established and effective initial therapy.[8] A recent meta-analysis by Brigo et al. brings forward data that suggests that PB could be more effective in terminating SE and in achieving seizure freedom 24 h after seizure cessation compared to other intravenous AEDs.[8,9] One small, retrospective single-center study investigating a cohort of 10 patients who received high doses of PB (≥10 mg/kg body weight) for SRSE, and achieved peak serum levels of ≥80 μg/mL, found a success rate of ~50% in terminating seizures, indicating that PB could be an effective tool for the treatment of SRSE.[10] Yet a 2022 survey among intensive care physicians demonstrated a profound reluctancy to initiate PB treatment for SE, with 50% of those questioned ranking PB as their fifth choice and ~25% declaring not to use the drug at all, which may reflect the fear of metabolic interactions or adverse drug events.[11]

The objective of this study was to investigate the efficacy and safety of PB in the treatment of SRSE in a retrospective, multi-center study design.

Key points

- Efficacy and safety of phenobarbital (PB) was analyzed retrospectively in 91 adults (age ≥18 y) with super-refractory status epilepticus (SRSE).
- Seizure termination was achieved in 54 patients (59.3%); successful treatment was associated with increasing serum levels.
- Functional outcome was better among patients in whom SRSE could be terminated, although the rates of favorable clinical outcome remained low.
- In-hospital mortality was significantly higher in patients in whom SRSE could not be terminated.
- Clinical complications during PB treatment affected 90% of patients in our cohort but did not affect functional outcome or in-hospital mortality.

2 | MATERIALS AND METHODS

2.1 | Study design

The present investigation is a retrospective, multi-center study of the Initiative for German NeuroIntensive Trial Engagement (IGNITE), a free alliance of German neurologists and neurosurgeons on neurointensive care units (NICUs) and subdivision of the German Society of Neurointensive and Emergency Care (DGNI).

2.2 | Patient recruitment

Patient recruitment was conducted in six participating centers. General eligibility criteria for inclusion were: (1) age ≥18 years, (2) diagnosis of SRSE between September 30, 2015, and September 30, 2020, and (3) enteral or parenteral PB treatment for SRSE. Patients with anoxic brain injury and patients in whom further AEDs were added after the first administration of PB were excluded from our analysis.

SRSE was defined as continuing or recurring SE after treatment failure of first- and second-line treatment

and ≥24 h of general anesthesia.[2] Status epilepticus (or SE) was defined as previously proposed by the International League Against Epilepsy (ILAE) Task Force in 2015 as an abnormally prolonged epileptic seizure of more than 5 min for tonic–clonic SE and 10 min for all other seizure types.[1]

2.3 | Data collection

Outcome parameters and clinical patient characteristics were gathered from patient data management systems of each center by the local subinvestigators and recorded in electronic case report forms on a secured server at the Ludwig-Maximilians-University of Munich. The case report forms were constructed via the web-application Research Electronic Data Capture (REDCap, Vanderbilt University, Tennessee, USA).

The primary outcome measure was seizure termination. SRSE was considered terminated if (1) confirmed on EEG and (2) no reoccurrence of SE was observed by the time participants were discharged from the NICU. Due to the retrospective study design, the latency between the first administration of PB and termination of SRSE was defined by the first routine EEG without SE. Functional outcome at discharge was assessed in the form of the modified Rankin scale (mRS).[12]

Preclinical physical condition was assessed using the premorbid modified Rankin scale (pmRS) and severity of SE was graded using the Epidemiology-based Mortality Score in Status Epilepticus (EMSE) and the Status Epilepticus Severity Score (STESS).[13–15] Recorded patient characteristics included the age in years on admission to hospital, sex, length of hospital stay in days, and in-hospital mortality. We assessed participants for their medical history of seizures and classified SE as proposed by the ILAE Task Force in 2015 for etiology and semiology.[1] Treatment parameters of interest included a history of AEDs; the choice of AEDs during hospitalization; their route of administration, dosage, and serum levels; and the composition and length of general anesthesia. We gathered PB serum levels over the time of hospitalization and documented the time of treatment induction relative to the diagnosis of SRSE. We furthermore screened for clinical complications in temporal relation with PB administration and assessed the rate of successful weaning from PB. Diagnostic parameters of interest included findings in imaging and EEG.

2.4 | Statistical methods

Statistical analysis was performed using IBM SPSS Statistics for Windows (Version 26.0; IBM Corp). Graphs were created using RStudio Team (2021, RStudio: Integrated Development Environment for R. RStudio, PBC). Results in univariate statistic measures for continuous variables are given in means and standard deviation (mean ± SD) or median and interquartile ranges (median [IQR]). Categorical variables are given as counts and percentages. Preselected parameters were tested for a statistically significant correlation with our primary outcome variable in univariate analysis (*t* test, Mann–Whitney *U*, chi-square test as best suited). Parameters were deemed statistically significant at $p < .05$. Parameters with $p < .1$ were retained for inclusion into a multivariate generalized linear model. STESS and EMSE were excluded from the multivariate model to avoid collinearity. Retained parameters were adapted for seizure semiology, age in years, and history of epilepsy. Missing values were included. The optimal threshold for PB serum levels predictive of seizure termination in our cohort was calculated using a receiver-operating characteristic (ROC) curve and determining Youden's J. We defined successful treatment as state variable and maximum PB serum level as test variable. True positive is defined as the rate of seizure termination at peak serum levels equal to or greater than Youden's J. The true negative rate describes the rate of PB peak serum levels below Youden's J, which were associated with treatment failure.

3 | RESULTS

3.1 | Demographics

Baseline characteristics are summarized in Table 1. Ninety-one patients were included in the final analysis of which 45.1% ($n = 41$) were female. The mean age at admission was 62.5 ± 16.3 years. Pre-hospitalization mRS scores ranged from 0 to 5, with a median of 2 [1–3]. Forty-one patients (45.1%) had a confirmed diagnosis of epilepsy prior to hospitalization, of which the majority (51.2%, $n = 21$) consisted of focal seizures. Generalized seizures were known in 26.8% ($n = 11$) of patients prior to hospitalization; 20.9% of patients ($n = 19$) in our cohort had a history of SE. Clinical severity of SE was at a median 3 [2–4] for STESS and 79.5 [65–105] for EMSE. The frequencies of each semiology and etiology of SE in our cohort are listed in Table 2. Most frequently, SE had an acute underlying cause (≤4 weeks; 42.9%, $n = 39$), followed by longstanding (>4 weeks; 30.8%, $n = 28$), progressive disease (e.g. brain tumor; 14.3%, $n = 13$), and electroclinical syndromes (2.2%, $n = 2$). The etiology of SRSE remained unknown in ~10% of patients ($n = 9$). In addition to PB, patients received 3 [2–3] AEDs. A detailed display of AEDs used before, during, and after PB treatment can be found in Table S1. A

TABLE 1 Baseline population and treatment characteristics.

	SRSE terminated ($n=54$)	Treatment failure ($n=37$)	Total ($n=91$)	p
Clinical characteristics at admission				
Age in years	61 [47–73]	73.0 [63–78]	62.5 (±16.3)	<.01
Female sex	28 (68.3)	13 (31.7)	41 (45.1)	.14
pmRS	2 [0–3]	3 [1–4]	2 [1–3]	.73
0	14 (25.9)	7 (18.9)	21 (23.1)	
1	5 (9.3)	3 (8.1)	8 (8.8)	
2	13 (24.1)	8 (21.6)	21 (23.1)	
3	8 (14.8)	9 (24.3)	17 (18.7)	
4	8 (14.8)	9 (24.3)	17 (18.7)	
5	2 (3.7)	1 (2.7)	3 (3.3)	
Missing	4 (7.4)	—	4 (4.4)	
STESS	3 [2–4]	4 [3–5]	3 [2–4]	<.01
EMSE	72 [60–91]	90 [72–116.5]	79.5 [65–105]	.01
Pre-existing epilepsy syndrome	23 (42.6)	18 (48.6)	41 (45.1)	.67
Focal	11 (47.8)	10 (55.6)	21 (51.2)	.45
Generalized	8 (34.8)	3 (16.7)	11 (26.8)	.51
Unknown	4 (17.4)	5 (27.8)	9 (21.9)	.33
History of SE	6 (11.1)	13 (35.1)	19 (20.9)	<.01
PB peak serum levels (μg/mL)	26.3 [16.3–37.2]	13.9 [7.6–20.7]	20.9 [10.7–34.8]	<.01
Number of additional AEDs	2.4±0.7	2.8±0.8	2.6±0.8	.06
Days to first PB administration	5.3 [3.6–13.0]	3.1 [1.2–6.3]	4.3 [2.0–10.7]	.21

Note: Results are given in counts (%), median [IQR] and mean±SD.

Abbreviations: AED, antiepileptic drug; EMSE, Epidemiology-based Mortality Score for Status Epilepticus; pmRS, pre-morbid modified Rankin scale; SE, status epilepticus; SRSE, super-refractory status epilepticus; STESS, Status Epilepticus Severity Score; PB, Phenobarbital.

frequency table of drugs used during general anesthesia preceding PB treatment can be found in Table S2.

3.2 | Treatment characteristics and efficacy of PB

Treatment characteristics and respective univariate p-values are summarized in Table 1. PB treatment was initiated after a median of 4.3 [2.0–10.7] days after the diagnosis of SE without a significant difference between groups. Seizure control was achieved in 54 cases (59.3%). The median number of days between diagnosis of SE and the first EEG without SE was 19.5 [9.8–31.7]. The median latency between the administration of PB and the first routine EEG without SE was 9.5 [6–19.3] days. Information on initial PB doses was missing in 10 patients. Among patients for whom information was available, initial PB doses appeared to be higher in patients in whom seizure control was achieved but the difference was not statistically significant (mg: 200 [150–550] vs 200 [200–215], $p=.86$). As for maintenance doses of PB, we observed significantly higher doses in patients in whom SRSE could be terminated (mg: 400 [200–500] vs 180 [180–212.5] $p<.01$; missing: $n=2$). Peak serum levels were reached within 8.0 [4.0–15.0] days across groups. PB serum levels differed significantly between groups (treatment failure: 14.0 [7,6 - 20,7] μg/mL vs successful treatment: 26.3 [16.3–37.2] μg/mL, $p<.01$).

Retained variables for multivariate analysis ($p<.1$ in univariate analysis) are displayed in Table 3. ROC curve analysis resulted in a threshold for PB peak serum levels predictive of seizure termination of 18.2 μg/mL with an area under the curve (AUC) of .73 (95% confidence interval [CI] = .63–.84) (Figure 1). In our multivariable analysis, successful treatment of SRSE was associated with increasing peak serum levels (per μg/mL: adjusted odds ratio [adj.OR] = 1.1, 95% CI = 1.04–1.15, $p<.01$) and

TABLE 2 Semiology and etiology of SRSE.

	SRSE terminated ($n=54$)	Treatment failure ($n=37$)	Total ($n=91$)	p
Semiology (ILAE 2015)				
Convulsive SE	15 (27.8)	7 (18.9)	22 (24.2)	.46
Nonconvulsive SE with coma	17 (31.5)	14 (37.8)	31 (34.1)	.65
Myoclonic SE	2 (3.7)	4 (10.8)	6 (6.6)	.22
Focal motor SE	10 (18.5)	2 (5.4)	12 (13.2)	.11
Focal non-convulsive SE w/o coma	10 (18.5)	10 (27.0)	20 (22.0)	.3
Etiology (most probable)				
Acute (≤4 weeks)	26 (48.1)	13 (35.1)	39 (42.9)	.28
Remote (>4 weeks)	16 (29.6)	12 (32.4)	28 (30.8)	.82
Progressive (e.g., brain tumor)	7 (13.0)	6 (16.2)	13 (14.3)	.76
Electroclinical syndrome	1 (1.9)	1 (2.7)	2 (2.2)	—[a]
Cryptogenic	4 (7.4)	5 (13.5)	9 (9.9)	.52
Etiology II				
Cerebrovascular	10 (18.5)	15 (40.5)	25 (27.5)	.03
Infectious	14 (25.9)	3 (8.1)	17 (18.7)	.05
Neurodegenerative disease	3 (5.6)	—	3 (3.3)	.27
Intracranial tumor	2 (3.7)	5 (13.5)	7 (7.7)	.12
Cortical dysplasia	2 (3.7)	—	2 (2.2)	.51
Traumatic brain injury	6 (11.1)	2 (5.4)	8 (8.8)	.46
Alcohol associated	2 (3.7)	2 (5.4)	4 (4.4)	—[a]
Metabolic imbalance or disease	2 (3.7)	2 (5.4)	4 (4.4)	—[a]
Autoimmune	6 (11.1)	1 (2.7)	7 (7.7)	.23
Mitochondrial disease	1 (1.9)	—	1 (1.1)	—[a]
Genetic	2 (3.7)	2 (5.4)	4 (4.4)	—[a]
Other/cryptogenic	4 (7.4)	5 (13.5)	9 (9.9)	.48

Note: Results are given in counts (%), median [IQR], and mean ± SD.

Abbreviations: SE, status epilepticus; SRSE, super-refractory status epilepticus; ILAE, International League Against Epilepsy.

[a]Due to the low number of patients the model could not be calculated.

significantly higher odds for patients with a threshold >18.2 μg/mL (adj.OR = 10.2, 95% CI = 3.0–34.5, $p < .01$). Increasing age was associated with a decreased odds of seizure termination (per age in years: adj.OR = .95, 95% CI = .91–.99, $p = .02$). An additional strong predictor of treatment failure was history of SE (adj.OR = .09, 95% CI = .01–.06, $p = .01$). We observed an association between cerebrovascular etiology and treatment outcome in our univariate analysis; however, this factor did not reach statistical significance when integrated into our multivariate model.

3.3 | Safety

A detailed display of clinical complications during PB treatment can be found in Table 4. Clinical complications during PB treatment occurred in 81 patients (89%). We observed large numbers of ICU-acquired infections ($n = 77$; 84.6%) without a significant difference between groups. Further clinical complications during PB treatment included hypotension requiring catecholamine therapy within 60 min after the first administration of PB ($n = 16$; 17.6%), anaphylactic shock ($n = 2$; 3.7%), and one case of

TABLE 3 The impact of retained variables on seizure termination.

	Multivariate OR	95% CI	*p*
PB serum levels per µg/mL	1.1	1.04–1.15	<.01
Number of AEDs (per AED)	.8	.4–1.7	.53
History of SE	.09	.01–.6	.01
Age in years (per year)	.95	.91–.99	.02
Etiology: cerebrovascular	.4	.1–1.6	.22
Etiology: infectious	1.5	.3–8.4	.64

Note: Adjusted for history of epilepsy and seizure semiology.

Abbreviations: 95% CI, 95% confidence interval; AED, antiepileptic drug; OR, odds ratio; PB, phenobarbital; SE = status epilepticus.

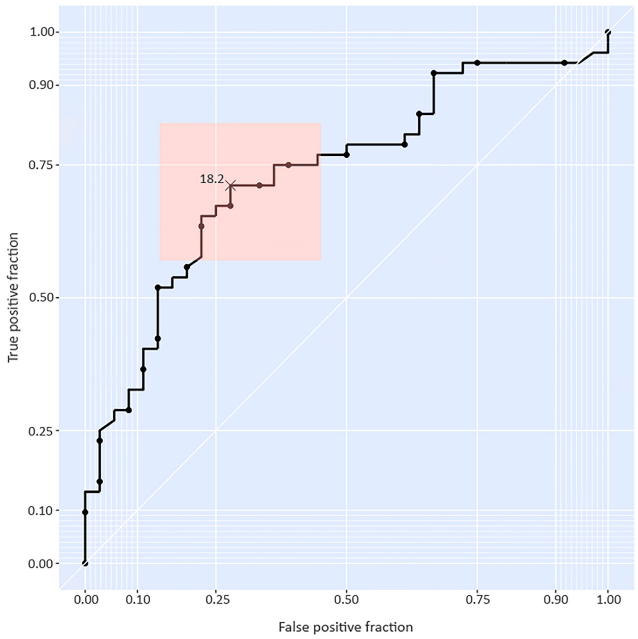

FIGURE 1 Phenobarbital serum levels and seizure termination in the receiver-operating characteristic curve. Receiver-operating characteristic curve for seizure termination depending on maximum phenobarbital serum levels. Youden's J is labeled x in the graphic; 95% confidence intervals for sensitivity and specificity are marked in pink.

Dupuytren's contracture. Hypotension requiring catecholamine therapy within 60 min after the first administration of PB was not associated with treatment outcome. Concerning anaphylactic shock and Dupuytren's contracture, case counts were too low to calculate a statistical model.

Neither the prevalence of any recorded complication nor the prevalence of ICU-acquired infections or hypotension requiring catecholamine therapy seemed to have a significant impact on mortality.

3.4 | Outcome

Outcome characteristics are summarized in Table 4. Across groups, the median time of hospitalization was 48.7 [31.3–65.9] days, of which patients spent 33.7 [23.2–56.6] days in the NICU. The length of NICU treatment in days did not differ significantly across group (34.4 [21.6–49.2] vs 32.5 [25.6–67.7], $p = .62$).

The mean mRS across groups was 5 ± 1. Six patients (6.6%) reached mRS ≤3, of which five were treated successfully with PB. We observed a statistically significant trend toward better functional outcome in patients in whom SRSE could be stopped ($p = .01$). In-hospital mortality was 9.5% ($n = 5$) for the group in which seizure control was achieved and 45.9% ($n = 17$) in the treatment failure group (adj.OR = 7.6, 95% CI = 2.2–25.9, $p < .01$). In addition, increasing age raised the odds for a fatal course of disease significantly (adj.OR = 1.1, 95% CI = 1.0–1.1, $p = .04$). Clinical complications did not impact mortality in univariate analysis (adj.OR = .8, 95% CI = .2–2.8, $p = .51$). Table 5 summarizes the impact of age, treatment failure, and history of SE on mortality.

4 | DISCUSSION

We observed high rates of seizure termination in patients with PB treatment for SRSE throughout our cohort, particularly in patients with elevated peak serum levels. Seizure control was achieved in 59% of patients and serum levels of PB >18 µg/dL increased the odds for seizure termination 10-fold. Clinical complications during PB treatment were common, affecting 90% of patients across groups; however, the incidence of clinical complications did not affect outcome and length of stay. Functional outcome was significantly better among patients in whom seizures could be terminated, although the rate of favorable outcomes (mRS ≤3) at discharge from the NICU remained low (~10% of treatment responders). In-hospital mortality (overall 24%) was significantly higher among patients in whom SRSE could not be stopped with an 8-fold odds of death.

Few studies have been conducted to investigate the efficacy of specific drugs for the treatment of SRSE. A study of 40 patients with SRSE treated with topiramate found that seizures could be terminated in 20% of patients after topiramate administration.[16] Similar results have been reported for treatment with brivaracetam and perampanel.[17,18] In a retrospective study of

TABLE 4 Clinical complications during treatment and outcome characteristics.

	SRSE terminated ($n=54$)	Treatment failure ($n=37$)	Total ($n=91$)	p
Clinical complications	48 (88.9)	33 (89.2)	81 (89.0)	.62
ICU-acquired infection	47 (87.0)	30 (81.1)	77 (84.6)	.56
Hypotension requiring catecholamine therapy within 60 min after first PB administration	8 (14.8)	8 (21.6)	16 (17.6)	.61
Anaphylactic shock	2 (3.7)	—	2 (2.2)	—[a]
Dupuytren's contracture	1 (1.8)	—	1 (1.1)	—[a]
Clinical outcome characteristics				
Seizure cessation	—	—	54 (59.3)	—
Length of SE in days (initial EEG – first EEG without SE)	19.5 [9.8–31.7]	—	19.5 [9.8–31.7]	—
Length of NICU stay in days	32.5 [25.6–67.7]	34.4 [21.6–49.2]	33.7 [23.2–56.6]	.30
Length of hospitalization in days	53.0 [34.5–78.2]	40.5 [25.2–57.0]	48.7 [31.3–65.9]	.2
Length of PB treatment until first EEG without SE in days	10.2 [6.7–19.8]	—	10.2 [6.7–19.8]	—
mRS at discharge from the NICU				.01
2	1 (1.9)	—	1 (1.1)	
3	4 (7.4)	1 (2.7)	5 (5.5)	
4	7 (13.0)	2 (5.4)	9 (9.9)	
5	37 (68.5)	17 (45.9)	54 (59.3)	
Death	5 (9.3)	17 (45.9)	22 (24.2)	<.01

Note: Results are given in counts (%), median [IQR], and mean ± SD.

Abbreviations: mRS, modified Rankin scale; NICU, neurointensive care unit; PB, phenobarbital; SE, status epilepticus; SRSE, super-refractory status epilepticus; EEG, Electroencephalography.

[a]Due to the low number of patients the model could not be calculated.

TABLE 5 The impact of age, clinical complications, and treatment failure on in-hospital mortality adapted for seizure semiology and history of seizures.

	Adj.OR	95% CI	p
Per years of age	1.1	1.0–1.1	.04
Treatment failure	7.6	2.2–25.9	<.01
History of SE	.3	.1–2.7	.34

Note: The impact of age and failure to terminate seizures on mortality adapted for seizure semiology and history of epilepsy.

Abbreviations: 95% CI, 95% confidence interval; adj.OR, adjusted odds ratio; SE, Status epilepticus.

68 consecutive patients with SRSE, an efficacy of 65% in terminating seizures was found for intravenous ketamine, although 41% of treatment responders deceased after ketamine cessation compared with 9% in the present cohort.[19] However, in other case series the efficacy of ketamine after weaning varies significantly between 28% and 96% of cases.[20] Intravenous pentobarbital as part of a suppression-burst pattern (SBP) anesthesia for at least 72 h has proven to be effective in terminating SRSE in a small retrospective study of 31 patients with an efficacy of 90% during anesthesia. However, weaning from pentobarbital anesthesia was associated with withdrawal seizures in 50% of patients and the authors reported to have added PB to the AED scheme to allow for successful weaning thereafter.[21] In conclusion there are data supporting the efficacy of ketamine and pentobarbital in achieving SBP but managing the risk of recurrence of seizures after weaning from the drugs poses a challenge. A recent retrospective multi-center study of 45 patients with refractory and super-refractory status epilepticus treated with isoflurane revealed an efficacy of 51% in terminating seizures permanently. However, comparability to our cohort may be reduced due to different patient collective with inclusion of earlier stages of SE.[22] As for PB, another case series of 10 young patients (mean age 38 years) with SRSE treated with a very high dose of PB (maximum serum PB level: median of 151.5 µg/mL) found an efficacy of ~50%.[10]

In our cohort we observed a correlation between increasing PB peak serum levels and successful treatment

of SRSE. This is also in line with the results of the above-mentioned case series by Byun et al. using ultra-high-dose regimens of PB.[10] Although this may seem intuitive, substantial data to determine which bandwidth of serum levels to aim for are still needed to balance efficacy and adverse drug reactions. In the collective at hand, peak serum levels ≥18.2 μg/mL were most reliably predictive of achieving seizure freedom, which may appear conservative, and the size of our cohort and study design do not allow for recommendations. The reported loading and maintenance doses in our cohort appear low, which may be an expression of the previously reported reluctancy among German neurointensivists to use barbiturates.[11] As with serum levels, we observed a correlation between higher daily doses of PB and treatment response. Given a seizure-cessation rate of 59% at low doses and thus relatively low serum levels of PB, the potency of PB to terminate seizures may be underestimated in our cohort.

In our study, the history and type of SE as well as etiology did not seem to influence the effectiveness of PB. In previous studies on SE or RSE, the history of epilepsy seems to predict efficacious medication response. However, our study focused on SRSE where the pathomechanisms for maintaining SE might be different, which limits comparability. Moreover, the size of our cohort does not allow further subgroup analysis.[23]

The median latency between the first administration of PB and the first EEG without SE was 9.5 days, which appears long. However, this measure is strongly limited by its dependency on routine EEG recordings due to the retrospective study design and the circumstance that continuous EEG recordings are regularly obtained in merely 50% of patients with SE in German NICUs and are often acquired at low resolution (less than eight channels in 60% of cases).[11] It is further limited by the fact that EEG recordings (routine and continuous) are widely unavailable outside of regular working hours to clinicians in Germany, where the study was conducted.[11] As a result, the latency between the initial trial of PB and the termination of SRSE is not depicted concisely. Nevertheless, EEG appears imperative to confirm the termination of SE.

Clinical complications over the course of PB treatment concerned 89% of patients but did not impact treatment efficacy significantly. ICU-acquired infections occurred in 87% of patients without a statistically significant difference between groups. One study investigating nosocomial infections in patients with SE requiring intensive care found a cumulative incidence of ~16% for ICU acquired infections, although it is not simple to compare to the prevalent cohort as the patients in that study remained in the ICU for a much shorter duration, with an average of 6.5 days compared to 33.7 days in our study.[24] The prevalence of ICU-acquired infections in the general patient population has been described to be as high as 47%, which is still much lower than the number we report.[25] However, methodological issues make comparisons among studies challenging. In a large worldwide study, 70% of ICU patients received at least one antibiotic during their ICU stay, with incidence being higher with higher extended stays.[26] Moreover, both central nervous system disease and barbiturates have been described to be predisposing factors to hospital-acquired infections. Central nervous system disease, for instance, is reported to increase the odds for the development of ventilator-associated pneumonia 3.5-fold, whereas the use of barbiturates is associated with a 2.7-fold increase.[27] Further clinical complications included two cases of anaphylactic shock and one case of Dupuytren's contracture, but case counts were too low to test for statistical significance. In the case of the patient who developed Dupuytren's contracture, we repeatedly observed PB serum levels ≥50 μg/mL.

It is noteworthy that neither clinical complications nor SE etiology had a significant impact on in-hospital mortality. Seizure termination was associated with a significant reduction of mortality, and ~10% of patients in whom SRSE could be terminated achieved good functional outcomes (mRS ≤3) vs 2% in the treatment-failure group. In conclusion, patients who were treated successfully for SRSE had significantly better functional outcomes at discharge from the ICU, although the rate of favorable outcomes (mRS ≤3) remained low. Unfortunately, few data exist with which to compare our results, since most studies that included patients with SRSE to evaluate the efficacy of a single drug for the treatment of SE also included patients with less severe forms of SE.[16–18] However, small retrospective studies that included exclusively patients with SRSE exist in the case of ketamine and pentobarbital.[19,21] For pentobarbital, the authors included 31 patients of whom 3% (n = 1) across groups had no or minimal disability at discharge from the ICU, whereas 55% were severely disabled or in a state of unresponsive wakefulness and the remaining 42% deceased during treatment.[21] In a retrospective study of patients with SRSE treated with ketamine, the authors reported a mean mRS of 5 ± 1 across groups at discharge from the ICU without any further detail.[19] A case series of 10 patients with SRSE treated with PB reported favorable outcomes in 20% of treatment responders, although these findings are limited by the low case count of the analysis.[10] Overall, our findings are similar to those made in the case of ketamine and pentobarbital, where the majority of patients displayed severe functional impairments at discharge from the ICU, although the lack of data on long-term outcomes is a certain limitation to these results. Considering a median length of ICU treatment of 34 days across groups, factors such as ICU-acquired weakness may play a significant role in the measure of mRS.

For instance, a prospective randomized controlled trial of 415 patients who received ICU treatment with a duration ≥8 days for any medical reason found signs of ICU-acquired weakness in 55% of patients at the time of initial assessment, and 6 min walking distance was obtainable in merely 28% of not weak and 14% of weak patients at discharge from the hospital.[28]

Mortality after successful termination of SRSE was low when compared to similar studies where mortality rates in treatment responders have been reported to be 22.6% for topiramate and 41% for ketamine compared to 9% in our cohort.[16,19] As for isoflurane, mortality independent of treatment outcome was reported 33% compared to 24% in the present study.[22] Of interest, mortality in our cohort was also much lower than in a multicenter French cohort, with similar characteristics, and a high rate of SRSE termination, where 52.5% of patients died.[29]

Some limitations of this study merit acknowledgment. We must admit a certain selection bias as all participating centers are referral centers for neurointensive care, possibly resulting in the inclusion of more severe cases. The present investigation is a retrospective study, allowing merely descriptive analysis. Route of administration, dosage, monitoring of PB treatment, and other therapeutic variables such as information on additional AEDs proved to be heterogeneous and missing in some cases. However, all sites used a standardized electronic Case Report Form (eCRF) with precise directives and definitions to minimize variability. Furthermore, due to the retrospective study design, we cannot selectively and definitively identify phenobarbital as the agent instrumental in terminating SRSE, since we cannot exclude the possibility that doses of other ongoing AEDs were adapted, for example, based on serum levels. However, these concomitant changes in additional medication do not account for the observed correlation between PB serum levels and seizure termination. The latency between PB administration and cessation of seizures was largely dependent on routine EEG due to reasons discussed previously, resulting in an imprecise measure of the length of SE. Moreover, PB was never initiated as first drug in our cohort, which is most likely an expression of a reluctancy to use barbiturates for the treatment of SE in Germany as reported in a survey by Kowoll et al. in 2022, in which 50% of questioned intensive care physicians ranked PB their fifth choice for the treatment of SE, whereas another 25% declared to never use PB at all.[11] In addition, we were not able to shed light on the long-term results and clinical outcomes of PB treatment for SRSE. The given outcome measures are limited to ICU treatment and, therefore, represent only a small snippet in an ongoing path to rehabilitation. With this study we also did not focus on weaning strategies of PB and can, therefore, not provide recommendations on long-term treatment strategies. Moreover, we cannot provide information about the etiology of in-hospital mortality. Another weakness of this study is the relatively low case count in a heterogeneous cohort of patients. Nevertheless, this study is presently the largest investigation of PB for the treatment of SRSE and, therefore, the most representative cohort to this point. SRSE is a rare and heterogeneous illness with few data to rely on for its management, making it difficult to further explore treatment options in prospective, randomized trials.

5 | CONCLUSION

We observed high efficacy of PB in the treatment of SRSE in our study. Increasing serum levels were associated with successful seizure termination. Besides reduced mortality, functional outcomes were significantly better in patients, although favorable outcome remained rare. Clinical complications are frequent but did not affect treatment outcomes negatively, and they were not associated with increased mortality.

AUTHOR CONTRIBUTIONS

PJO and MA made substantial contributions to this study in terms of data acquisition. PJO revised the manuscript at hand and contributed to data interpretation. MJ and ML made major contributions to this work in terms of data acquisition. MD and RC revised the manuscript and made important contributions in terms of data acquisition and interpretation of the data. MMi, MM, and NB contributed substantially in terms of data acquisition. KS designed the eCRF, and contributed in data collection, analysis, and interpretation. KS drafted the work. SML and KS contributed to the eCRF, and analysis and interpretation of the data. Moreover, they substantially revised the manuscript. RM was a major contributor in the acquisition of data. All authors have approved the final manuscript including the authors' contribution to the study and agree to be personally accountable for the author's own contributions and to ensure that questions related to the accuracy or integrity of any part of the work, even ones in which the author was not personally involved, are appropriately investigated and resolved, and the resolution documented in the literature.

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CONFLICT OF INTEREST STATEMENT

None of the authors has any conflict of interest to disclose. We confirm that we have read the Journal's position on

issues involved in ethical publication and affirm that this report is consistent with those guidelines.

DATA AVAILABILITY STATEMENT

The data sets used and analyzed during the current study are available from the corresponding author on reasonable request.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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