■ Original article

Epileptic Disord 2021; 23 (6): 833-842

Epileptic Disorders

Pentobarbital coma therapy for super-refractory status epilepticus and in-hospital mortality: an observational study

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Received February 22, 2021;
Accepted April 26, 2021

ABSTRACT

Objective. Treatment of super-refractory status epilepticus (SRSE) is associated with various complications of anaesthetic coma therapy. This study aimed to describe the factors affecting the prognosis, especially in-hospital mortality, of patients receiving pentobarbital coma therapy for the treatment of SRSE.

Methods. This was a retrospective cohort study conducted in a single tertiary referral centre with patients who received pentobarbital coma therapy for the treatment of SRSE from 2006 to 2018. Exploratory analyses were performed for clinical, laboratory, electrographic, and radiological factors for the entire cohort and were compared between the mortality and survivor groups.

Results. In total, 19 patients were enrolled, and five (26.3%) patients died in the hospital. The maximal pentobarbital infusion dose was higher in the mortality group than in the survivor group (4.4±1.0 mg/kg/h vs. 2.9±1.4 mg/kg/h, respectively; p=0.025). The high-dose pentobarbital infusion group (>3.75 mg/kg/h) underwent longer mechanical ventilation (24 [20–36.75] vs. 41 [28–70], p=0.025) and blood culture results were more frequently positive, suggestive of septicaemia (8.3% vs. 57.1%, p=0.038).

Significance. The group of SRSE patients treated with pentobarbital coma therapy who died in the hospital received a higher pentobarbital infusion dose compared to survivors; a complication of high-dose pentobarbital infusion was septicaemia. Considering the high rate of septicaemia observed, systematic treatment strategies focusing on infectious complications should be established and implemented. The association between maximal pentobarbital infusion dose and in-hospital mortality needs to be further validated.

Key words: super-refractory status epilepticus, pentobarbital coma therapy, pentobarbital infusion dose, prognosis

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doi:10.1684/epd.2021.1333

Super-refractory status epilepticus (SRSE) is defined as persistent seizures despite therapeutic coma using continuous infusion of intravenous (IV) anaesthetic agents for 24 hours or recurrence of seizures upon reduction or withdrawal of the agents [1]. The mainstay of SRSE treatment is to continue the therapeutic coma, with additional treatment options including magnesium infusion, the ketogenic diet, and electroconvulsive therapy, although the utility of these approaches lacks evidence [2]. Therapeutic coma typically requires aggressive and prolonged treatment in the intensive care unit (ICU) and is associated with multiple medical and surgical complications. The prognosis of SRSE is variable, with an in-hospital mortality rate of 10-42% [3-5], but full recovery can

also be expected [6]. Previous studies have identified several prognostic factors for SRSE, including age and premorbid functional status [7].

To date, no specific IV anaesthetic agent used in coma therapy has demonstrated overall superiority. However, pentobarbital exhibits fairly strong antiseizure effects [1]. Pentobarbital coma therapy was reported to result in 90% seizure termination in patients with SRSE [5]. Pentobarbital exerts potential neuroprotective effects and reduces intracranial pressure, and is one of the most commonly used IV anaesthetic drugs [8]. Its side effects include cardiorespiratory depression, paralytic ileus, immunosuppression, electrolyte imbalance, hepatic dysfunction, and peripheral neuropathies [9, 10]. Several prognostic factors of pentobarbital coma therapy have been identified, including complications such as hypotension, prolonged coma, and prolonged mechanical ventilation [11].

Only a few studies have addressed the prognosis and its associated factors in SRSE patients treated with pentobarbital coma therapy. Therefore, this study aimed to further describe the clinical factors affecting future prognosis, especially in-hospital mortality, in SRSE patients treated with pentobarbital coma therapy.

Materials and methods

Patients

A retrospective review of all consecutive status epilepticus (SE) patients admitted to Ajou University Hospital from January 2006 to December 2018 was performed. The data were retrospectively collected by comprehensively reviewing patients' electronic medical records. SE caused by potentially fatal aetiologies, such as post-cardiac arrest hypoxic-ischemic encephalopathy, traumatic brain injury, and malignant strokes resulting in increased intracranial pressure and herniation, was excluded [12]. Of all SE patients, refractory status epilepticus (RSE) patients who received continuous IV anaesthetic therapy were selected. Of these patients, those who received pentobarbital coma therapy were included in the final analyses. SRSE was defined as an ongoing clinical seizure or documented EEG seizure during continuous EEG monitoring, persisting or recurring after a coma therapy. Ethics approval was obtained from the local institutional review board, and the board waived the need for patient consent (AJIRB-MED-MDB-19-438).

Institutional SE treatment protocol

All patients were initially treated with IV benzodiazepine. Second-line antiseizure drugs (ASDs) were selected among levetiracetam, fosphenytoin or phenytoin, and valproate. Patients who were commenced on coma therapy underwent continuous EEG monitoring or received a routine EEG test for 30 minutes, at least twice a day. All patients underwent diagnostic studies, including computed tomography or brain MRI, serologic studies, and CSF studies on the day of admission. Midazolam, pentobarbital, ketamine, and propofol were used as therapeutic agents for continuous infusion therapy. The selection of IV agents was based upon each individual's clinical situation. For patients who received coma therapy using multiple agents, those who were administered pentobarbital were enrolled for the analyses. Pentobarbital was administered at a 10-mg/kg loading dose and maintained with continuous infusion starting from 0.5 mg/kg/h. The dosage was subsequently escalated according to the EEG. All patients receiving coma therapy were admitted to a neuro-ICU and received ventilator support via endotracheal mechanical ventilation.

The goal, regarding the extent of sedation, was either electrical seizure suppression or burst suppression. If the seizure persisted after the induction of burst suppression, patients were sedated until isoelectricity was attained. Tapering of the anaesthetic agent was performed carefully, at least 48 hours after the attainment of seizure cessation, during which coma therapy was resumed until the seizure was suppressed again in the event of a withdrawal seizure.

Alongside continuous IV coma therapy, immunotherapy, such as steroid pulse therapy, intravenous immunoglobulin G (IVIG), plasma exchange, rituximab, or tocilizumab therapy, were implemented if limbic encephalitis or autoimmune encephalitis were suspected. Additional non-anaesthetic treatment strategies for SRSE, such as IV magnesium infusion, electroconvulsive therapy, and the ketogenic diet, were also implemented when considered adequate.

Definitions and classifications

The classification of semiology and aetiology was based on previous literature, with modifications [13]. SE semiology was classified into three groups based on the initial manifestation of SE: focal, generalized convulsive, and non-convulsive SE. EEG findings prior to coma therapy were classified into two groups: ongoing ictal discharges or intervening periodic discharges. SE aetiology was categorized into three groups: acute symptomatic, remote symptomatic, and cryptogenic. New-onset refractory SE (NORSE) was defined as refractory SE in previously healthy individuals without a clear acute or active structural, toxic, or metabolic cause [14]. Status Epilepticus Severity Score (STESS) was determined according to a previous study [15]. The maximal pentobarbital infusion dose was defined as the maximally increased maintenance dose

that was considered effective for seizure suppression for at least 48 hours.

Variables and statistical analysis

Basic demographics, the Charlson comorbidity index [16], STESS, semiology, aetiology, and EEG correlates were analysed. The primary treatment outcome was in-hospital mortality and based on the modified Rankin scale (mRS) at the time of discharge and at three months of follow-up. In-hospital mortality was set as the primary outcome.

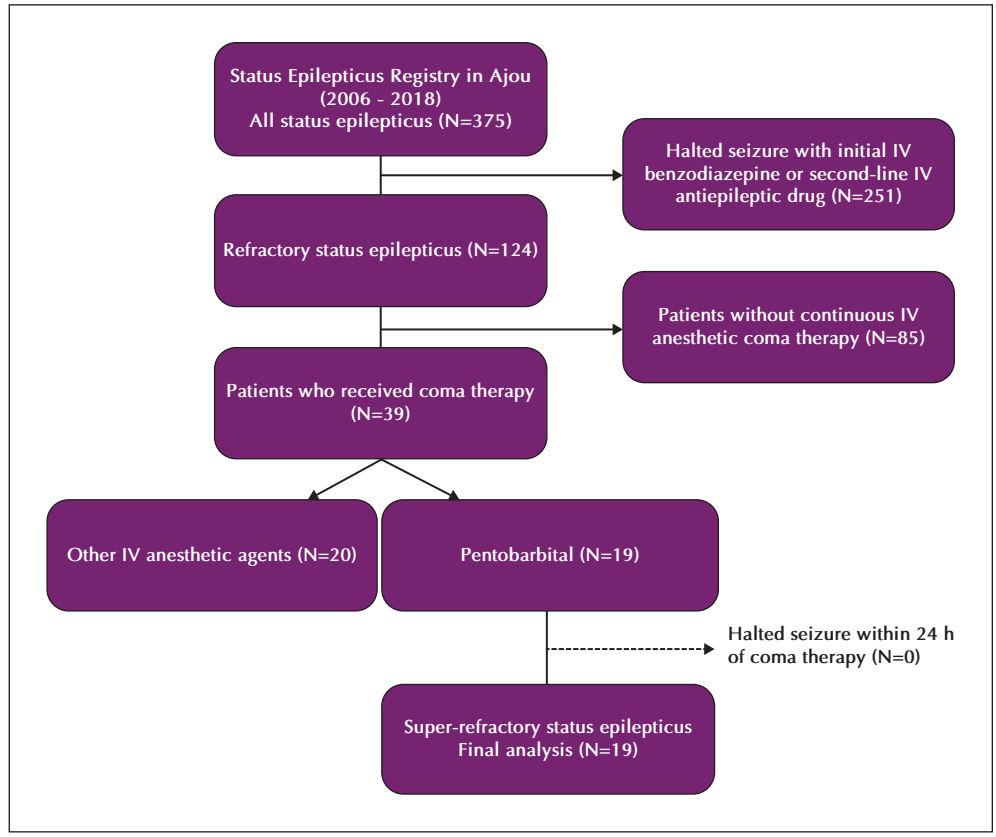
Variables were expressed as numbers (percentage), mean ± standard deviation, and median (interquartile range [IQR]) values. Continuous variables were compared using the Mann-Whitney U test. Categorical variables were compared using the Fisher's exact test or the Chi-squared test. Receiver operating characteristic (ROC) analysis was performed to generate a cut-off value of maximal pentobarbital infusion dose. Due to the small sample size and a large number of variables, multivariate analysis was not performed. IBM SPSS Statistics for Windows, version 25.0 (IBM Corp., Armonk, NY, USA) and R version 3.6.3, were used for statistical analyses. Statistical significance was defined as $p < 0.05$.

Results

Patient demographics

From 2006 to 2018, 375 SE patients were admitted to our institution. Of these, 124 (33.1%) were categorized as having RSE, and 39 (10.4%) patients received coma therapy using continuous IV anaesthetic agents. Of the 39 patients receiving therapeutic coma treatment, 19 (48.7%) received pentobarbital. Of these patients, 11 (57.9%) received pentobarbital as the first-line infusion agent. *Figure 1* presents a summary of the patient selection process included in the analyses.

Table 1 summarizes the clinical and SE characteristics, test results, treatments, and outcomes. Patients were previously healthy, as indicated by a median Charlson's comorbidity index of 0 (IQR: 0-1). Fifteen patients (78.9%) were compatible with the definition of NORSE. Seventeen patients (89.5%) were classified as having acute symptomatic SE, and most of these (82.4%) were



■ **Figure 1.** Flowchart of patient selection.

▼ **Table 1.** Overview of basic demographics and clinical characteristics.

Variables	No. (%) or median [IQR]
Male	12 (63.2)
Age	45 [32–51]
Charlson's comorbidity index	0 [0–1]
STESS	3 [2–3]
NORSE	15 (78.9)
Acute symptomatic aetiology	17 (89.5)
Semiology	
Focal SE	5 (26.3)
GCSE	8 (42.1)
NCSE	6 (31.6)
EEG before coma therapy	
Continuous ictal discharges	10 (52.6)
Intervening periodic discharges	9 (47.4)
Number of used ASDs	2 [2–3]
Coma induction within 24 h	3 (15.8)
Coma therapy duration > 7 days	14 (73.7)
Pentobarbital as the first-line infusion agent	11 (57.9)
Maximal pentobarbital infusion dose (mg/kg/h), mean±SD	3.3±1.5
EEG during coma therapy	
Burst-suppression	16 (84.2)
Isoelectricity	3 (15.8)
Immunotherapy	
Steroid-pulse therapy	16 (84.2)
Intravenous immunoglobulin G	15 (78.9)
Plasma exchange	3 (15.8)
Rituximab	5 (26.3)
Use of neuromuscular blocking agent	2 (10.5)
Use of inotropes	9 (47.4)
Positive blood culture test during coma therapy	5 (26.3)
Length of stay (days)	
ICU stay	37 [27–57]
Hospital stay	58 [37–103]
Period under mechanical ventilation	27 [21–48]
Tracheostomy	9 (47.4)
Outcome	
In-hospital mortality	5 (26.3)
mRS at discharge	3 [2–6]
Good outcome (mRS: 0-2) at discharge	7 (36.8)
mRS at 3 months	3 [2–6]

ASD: antiseizure drugs; EEG: electroencephalogram; GCSE: generalized convulsive status epilepticus; ICU: intensive care unit; IQR: interquartile range; mRS: modified Rankin scale; NCSE: non-convulsive status epilepticus; NORSE: new-onset refractory status epilepticus; SE: status epilepticus; STESS: Status Epilepticus Severity Score.

subsequently diagnosed with probable autoimmune encephalitis. In all patients, burst-suppression EEG was achieved, and three patients were sedated until isoelectricity was attained.

In total, five (26.3%) patients died in the hospital. The direct causes of death differed among patients: four died of sepsis and one had a sudden cardiac arrest. Seven (36.8%) were discharged with good outcome (mRS: 0-2). The median value for the three-month mRS was 3 (IQR: 2-6). A brief description of the treatment course of patients in this study is summarized in *table 2*.

In-hospital mortality

The comparison between the survivor and mortality groups is summarized in *table 3*. No significant differences were observed in baseline demographics, aetiology, semiology, severity, or EEG correlates between the survivor and mortality groups. Moreover, no significant differences were noted in major side effects of pentobarbital, such as dyskalaemia, use of inotropes, positive blood culture tests, and serum C-reactive protein (CRP) levels between the survivor and mortality groups.

Pentobarbital infusion dose was significantly higher in the mortality group than in the survivor group (4.4 ±1.0 mg/kg/h vs. 2.9±1.4 mg/kg/h, p=0.025). No significant between-group differences were observed in the timing of pentobarbital induction, duration of coma, or extent of sedation on EEG. Additional analysis revealed that pentobarbital infusion dose was higher in the poor outcome group, represented by an mRS score of 4-6 at discharge (4.4±1.4 mg/kg/h vs. 2.5±1.0 mg/kg/h). A violin plot depicting the maximal pentobarbital infusion doses for the survivor and mortality groups is presented in *figure 2*.

Based on the significantly higher pentobarbital infusion dose in the mortality group, further analysis was performed. Maximal pentobarbital infusion dose was dichotomized using a cut-off value of 3.75mg/kg/h, and the high-dose and low-dose groups were compared. The cut-off dose was generated based on the ROC analysis. The high-dose pentobarbital group (>3.75 mg/kg/h) was associated with longer mechanical ventilation (24 [20–36.75] vs. 41 [28–70], p=0.025) and more frequent positive blood culture tests, suggesting septicaemia (8.3% vs. 57.1%, p=0.038) when compared to the low-dose group.

Discussion

This retrospective study explored the factors affecting mortality associated with pentobarbital coma therapy for SRSE. In the present study, we observed that maximal pentobarbital infusion dose was higher in the in-hospital mortality group, compared to survivors.

During pentobarbital coma therapy for SRSE, multiple life-threatening complications have been reported with the use of pentobarbital itself, including cardio-respiratory depression, infection, and dyskalaemia. There has been controversy regarding whether coma therapy itself is independently associated with poorer outcomes and in-hospital mortality [17-19]. Further, the risks associated with pentobarbital use have been highlighted in numerous studies [20, 21]. Compared to other IV anaesthetic agents, pentobarbital is associated with a longer duration of hospital stay and longer period under mechanical ventilation [20, 21].

Pentobarbital exhibits zero-order kinetics and therefore accumulates in the body, especially with continuous infusions [1]. The lower elimination rate of pentobarbital with higher dose infusions results in side effects in a dose-dependent manner. Hypotension and autonomic responses induced by pentobarbital administration have been well documented in animal experiments [22]. Further, immunosuppression and subsequent risk of infection may result from the pentobarbital-induced reduction of phagocytic activity, inhibition of peripheral lymphocyte function, and suppressed neutrophil migration [10, 23]. This is supported by our data from the high-dose pentobarbital group, which demonstrated a higher rate of positive blood culture tests.

Due to the side effects of pentobarbital, determining the appropriate dose for each patient is crucial. The therapeutic dose for pentobarbital coma therapy (0.5–5 mg/kg/h) is supported by clear evidence [24]. Within this window, dose adjustments are based on continuous EEG monitoring, according to the "pentobarbital demand" by each seizure. As breakthrough seizures are often observed even in the burst-suppression state, the demand is commonly high in these SRSE patients. Measurement of serum concentration of pentobarbital is not readily available in all hospitals due to a lack of commercially available automated assays to determine pentobarbital levels [25]. In addition, due to pharmacodynamic tolerance and multiple concomitant ASDs resulting in drug interactions, it has been considered impractical to define and maintain therapeutic ranges according to serum concentrations [26].

The overall outcome measures observed in our study are consistent with previous results. Despite an in-hospital mortality rate of 26.3%, good discharge outcomes (mRS: 0–2) were observed in 36.8% of the patients. Life-threatening complications associated with pentobarbital were observed in survivors and were successfully treated. Survivors and patients with good outcomes were identified in the high-dose pentobarbital group. Notably, the high-dose group

▼ **Table 2.** Brief description of patients underwent pentobarbital coma therapy in the study.

Patient		Aetiology	STESS	NORSE	Before coma therapy			During coma therapy				Immunotherapy	Outcome of coma therapy					
					Semiology	EEG	ASD No	Agents used (in order)	Pentobarbital dose (mg/kg/h)	EEG	Duration (days)		Inotropes	CRP (mg/dL)	MV (days)	Hospital (days)	mRS at discharge	Cause of death
1	F/51	Probable AE	3	Yes	GCSE	ASID	2	Midazolam → Pentobarbital	2.0	BS	4	Pulse, IVIG	Dopamine	Not studied	20	43	2	-
2	F/47	Probable AE	3	Yes	Focal SE	ASID	2	Pentobarbital	3.5	BS	22	Pulse, IVIG	Dopamine	9.58	27	71	3	-
3	M/51	Probable AE	3	Yes	GCSE	ASID	1	Midazolam → Pentobarbital	2.5	BS	117	Pulse, IVIG	None	12.07	99	131	5	-
4	F/41	Probable AE	3	Yes	NCSE	Bi-LPD, ASID	2	Midazolam → Pentobarbital	4.5	BS	32	Pulse, IVIG	None	1.13	41	66	2	-
5	F/39	Probable AE	3	Yes	GCSE	ASID	0	Pentobarbital	2.5	BS	31	Pulse, IVIG	None	3.44	40	82	3	-
6	M/34	Probable AE	3	Yes	GCSE	ASID, Bi-LPD	2	Midazolam → Pentobarbital	4.5	BS	97	Pulse, IVIG, PEX	None	11.89	103	103	6	Sepsis
7	M/32	Probable AE	3	Yes	GCSE	GPD, ASID	1	Midazolam → Pentobarbital	4.0	BS	60	Pulse, IVIG, PEX	None	12.44	70	127	4	-
8	M/27	Probable AE	3	Yes	NCSE	ASID, GPD	2	Pentobarbital	2.0	BS	28	Pulse, IVIG, PEX	None	2.72	48	196	2	-
9	F/49	Probable AE	2	Yes	Focal SE	ASID, RDA	2	Pentobarbital	5.0	BS	58	Pulse, IVIG	Dopamine	24.68	69	181	6	Sepsis
10	M/45	Remote ICH	3	No	GCSE	Bi-LPD	2	Pentobarbital	3.0	BS	14	None	None	3.87	20	48	2	-
11	M/23	Probable AE	2	Yes	NCSE	Bi-LPD, ASID	1	Pentobarbital	6.7	BS	30	Pulse, IVIG, Rituximab	Dopamine	0.09	25	35	5	-
12	M/46	Probable AE	2	Yes	GCSE	Bi-LPD, ASID	2	Midazolam → Propofol → Pentobarbital	1.0	BS	5	Pulse, IVIG, Rituximab	None	0.1	26	53	3	-
13	M/66	Cavernous malformation	3	No	NCSE	ASID	3	Midazolam → Propofol → Pentobarbital	3.0	BS	9	None	NE	3.49	16	32	2	-
14	M/62	Probable AE	3	No	Focal SE	LPD, BS	3	Midazolam → Pentobarbital	2.0	I	6	Pulse, IVIG	Dopamine	5.3	25	87	3	-

▼ **Table 2.** Brief description of patients underwent pentobarbital coma therapy in the study (*continued*).

15	M/ 37	Probable AE	2	Yes	NCSE	ASID	2	Midazolam → Pentobarbital	2.0		BS	17	Pulse, IVIG, Rituximab	None	0.66	21	48	2	-
16	M/ 53	Probable AE	3	Yes	Focal SE	ASID	3	Midazolam → Propofol → Pentobarbital	4.0		BS	4	Pulse, IVIG, Rituximab	None	5.23	28	30	6	Sepsis
17	M/ 21	Probable AE	2	Yes	GCSE	ASID, BS	4	Midazolam → Pentobarbital → Ketamine → Propofol	5.5		I	33	Pulse	NE	0.55	38	37	6	Sepsis
18	F/ 20	Probable AE	1	Yes	Focal SE	ASID	6	Midazolam → Pentobarbital → Ketamine	2.0		BS	20	Pulse, IVIG, Rituximab, Tocilizumab	NE	2.11	23	58	1	-
19	F/ 73	Remote SAH	6	No	NCSE	ASID	2	Pentobarbital	3.0		I	3	None	NE	26.03	11	21	6	Sudden cardiac arrest

AE: autoimmune encephalitis; ASD: antiseizure drugs; ASID: after status ictal discharge; Bi-LPD: bilateral independent lateralized periodic discharge; BS: burst suppression; CRP: C-reactive protein; CSF: cerebrospinal fluid; GCSE: generalized convulsive status epilepticus; GPD: generalized periodic discharge; I: isoelectricity; ICH: intracerebral hemorrhage; IVIG: intravenous immunoglobulin G; mRS: modified Rankin scale; MV: mechanical ventilation; NE: norepinephrine; NCSE: non-convulsive status epilepticus; No: number; NORSE: new-onset refractory status epilepticus; PEX: plasma exchange; Pulse: steroid pulse therapy; RDA: rhythmic delta activity; SAH: subarachnoid hemorrhage; SE: status epilepticus; STESS: Status Epilepticus Severity Score.

did not demonstrate the features associated with greater CNS suppression or cardiovascular depression, represented by isoelectric EEG and inotrope use. Further studies to identify patients who tolerate high-dose pentobarbital are necessary for patient selection for appropriate SRSE treatment.

The retrospective nature of our study limits the interpretation of the findings. Although the pentobarbital infusion dose was higher in the mortality group, this does not explain the nature of the association between the pentobarbital infusion dose and mortality. It remains unclear whether a higher dose of pentobarbital and the associated side effects were the cause of mortality. An alternative explanation is that the demand for pentobarbital was higher in patients with more severe SRSE. Nevertheless, it can be inferred that the risk of infection was increased due to a higher pentobarbital dose because the cause of deaths in most patients was sepsis, and positive blood culture tests were more frequently observed in the high-dose pentobarbital group. Considering the earlier induction of coma and more intensive dose-escalation precipitated by severe SRSE, the critical factor for the complications observed in our patients was the fatality associated with septicaemia.

Previously identified prognostic factors such as age, aetiology, and premorbid condition did not affect prognosis in our cohort. However, it is unlikely that this negative result was a major confounder in the interpretation of our findings. Instead, this finding could be underpinned by the homogeneity of our population. The patients were younger, premorbidly healthier, and had non-potentially fatal SRSE aetiologies. Potentially fatal aetiologies, such as post-cardiac arrest hypoxic-ischemic encephalopathies, were not included in our initial cohort. Further, the majority of our patients presented with NORSE and were subsequently diagnosed with probable autoimmune encephalitis. In this regard, the characteristics of the current cohort more closely resemble the recently introduced "new-onset super-refractory status epilepticus (NOSRSE)" population [27].

Another limitation of our study is the small sample size and long recruitment period. During the study period, the criteria for patient selection for coma therapy and sensitivity for the detection of NCSE changed. Many RSE patients who did not receive IV coma therapy were excluded from the analysis; these patients could have benefitted from the treatment. Further, with the advancements in immunotherapy modalities for NORSE, the need to use highly potent agents such as pentobarbital is diminished. Trends in managing complications occurring in the neuro-ICU have also developed, such as the definition, recognition, and treatment of sepsis. For this, larger-scale, uniform, prospective studies are required to confirm the

▼ **Table 3.** Comparison of clinical parameters between the survivor and mortality groups.

	Survivor (*n*=14)	Mortality (*n*=5)	*p* value
Patient factors			
Male, number (%)	9 (64.3)	3 (60.0)	0.865
Age, median [IQR]	43 [30.75–51]	49 [27.5–63]	0.578
Charlson's comorbidity index, median [IQR]	0 [0–1.25]	0 [0–4]	0.789
CSF cell (number/μL), median [IQR]	3.5 [2.0–14.25]	12 [0–17.5]	0.832
CSF protein (mg/dL), mean±SD	46.62±13.47	126.62±152.63	0.460
Seizure factors			
STESS, median [IQR]	3 [2–3]	3 [2–4.5]	0.829
NORSE, number (%)	13 (92.9)	5 (100)	>0.999
Acute symptomatic aetiology, number (%)	13 (92.9)	4 (80.0)	0.468
Semiology			
Focal SE, number (%)	3 (21.4)	2 (40.0)	0.819
GCSE, number (%)	6 (42.9)	2 (40.0)	
NCSE, number (%)	5 (35.7)	1 (20.0)	
EEG before coma therapy			
Continuous ictal discharges, number (%)	7 (50.0)	3 (60.0)	>0.999
Intervening periodic discharges, number (%)	7 (50.0)	2 (40.0)	>0.999
Treatment factors			
Number of used ASDs	2 [1–2.25]	2 [2–3.5]	0.209
Coma induction within 24 h, number (%)	1 (7.1)	2 (40.0)	0.155
Coma therapy > 7 days, number (%)	11 (78.6)	3 (60.0)	0.570
Pentobarbital as the first-line infusion agent, number (%)	6 (42.9)	2 (40.0)	>0.999
Maximal pentobarbital infusion dose (mg/kg/h), mean±SD	2.91±1.43	4.40±0.96	0.025
Isoelectric EEG during coma therapy, number (%)	1 (7.1)	2 (40.0)	0.058
Use of neuromuscular blocking agent, number (%)	1 (7.1)	1 (20.0)	0.468
Immunotherapy			
Steroid pulse therapy, number (%)	12 (85.7)	4 (80.0)	>0.999
Intravenous immunoglobulin G, number (%)	12 (85.7)	3 (60.0)	0.272
Plasma exchange, number (%)	2 (14.3)	1 (20.0)	>0.999
Rituximab, number (%)	4 (28.6)	1 (20.0)	>0.999
Length of stay			
Hospital days, median [IQR]	62 [46.75–97]	37 [25.5–142]	0.405
ICU days, median [IQR]	37 [25.75–46.5]	37 [24.5–142.5]	0.781
Mechanical ventilation days, median [IQR]	25.5 [20.75–42.75]	38 [19.5–86]	0.404
Tracheostomy, number (%)	8 (57.1)	1 (20.0)	0.303
EEG during coma therapy			
Burst-suppression, number (%)	13 (92.9%)	3 (60.0%)	0.155
Isoelectricity, number (%)	1 (7.1%)	2 (40.0%)	
Complications			
Use of inotropes, number (%)	6 (42.9)	3 (60.0)	0.628
Dopamine use, number (%)	4 (28.6)	1 (20.0)	>0.999
Norepinephrine use, number (%)	2 (14.3)	2 (40.0)	0.272
Positive bloodstream culture test during coma therapy, number (%)	3 (21.4)	2 (40.0)	0.570
Maximal CRP within 3 days of coma, mean±SD	4.39±4.31	13.68±11.41	0.144
Hypokalemia, number (%)	2 (14.3)	2 (40.0)	0.272
Hyperkalemia, number (%)	1 (7.1)	1 (20.0)	0.468

Values are presented as numbers (percentage), mean ± standard deviation, or median [interquartile ratio].
ASD: antiseizure drugs; CRP: C-reactive protein; GCSE: generalized convulsive status epilepticus; IQR: interquartile range; NCSE: non-convulsive status epilepticus; NORSE: new-onset refractory status epilepticus; SE: status epilepticus; STESS: Status Epilepticus Severity Score.

■ **Figure 2.** Violin plot of maximal pentobarbital infusion doses in the survivor and mortality groups. Each dot represents a patient, and the colour of the dots represents the modified Rankin Scale (mRS) at discharge.

generalizability of our findings. The interpretation of the maximal pentobarbital infusion dose as a risk factor for in-hospital mortality presented in this study should not be considered conclusive.

During the administration of pentobarbital coma therapy for the treatment of SRSE, the adjustment of pentobarbital infusion dose was mainly driven by EEG. However, this was complicated by hypotension and infectious complications that occurred with the prolongation of the treatment period. Treatment strategies avoiding toxicity should be considered. For instance, add-on therapy using other IV anaesthetic agents or additional non-anaesthetic modalities could be implemented. The outstanding complications in our patients were septicaemia; therefore, close monitoring of emerging signs of infection and appropriate antibiotic therapy should be used in combination when treating SRSE. However, this interpretation should be taken cautiously with regard to the limitations of the study.

Conclusion

In SRSE patients treated with pentobarbital coma therapy, a higher pentobarbital infusion dose was observed in the in-hospital mortality group compared to survivors. Although there was no significant difference in the rate of previously known complications associated with pentobarbital coma therapy, patients who received a higher pentobarbital infusion dose showed more septicaemia and required a longer mechanical ventilation period. Organized treatment strategies should be implemented to avoid pentobarbital toxicity. Further large-scale prospective studies are required to verify our findings. ■

Supplementary material.
Summary slides accompanying the manuscript are available at www.epilepticdisorders.com.

Disclosures.
The authors declare that they have no competing interests.
This research was supported by the National Research Foundation (NRF) funded by the Korean government (MSIT) (NRF-2018M3A9E8023853, NRF-2018R1C1B6006145, NRF-2019R1A5A2026045 and HI19C1044).

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TEST YOURSELF

(1) What are the previously known major side effects associated with pentobarbital coma therapy for super-refractory status epilepticus?

(2) How does pentobarbital infusion therapy affect the immune system, and therefore complicate the course of treatment?

(3) Based on this study, what kind of complication should be carefully monitored during pentobarbital coma therapy?

Note: Reading the manuscript provides an answer to all questions. Correct answers may be accessed on the website, www.epilepticdisorders.com.