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Observed medical and surgical complications of prolonged barbiturate coma for refractory status epilepticus

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Abstract

Background: Refractory status epilepticus is often treated with third-line therapy, such as pentobarbital coma. However, its use is limited by side effects. Recognizing and preventing major and minor adverse effects of prolonged pentobarbital coma may increase good outcomes. This study retrospectively reviewed direct and indirect medical and surgical pentobarbital coma.

Methods: Retrospective chart review of all patients with refractory status epilepticus treated with pentobarbital over a 1 year period at a large tertiary care center. We collected baseline data, EEG data, and complications that were observed.

Results: Overall, nine patients [median age 46.4 (IQR 21.7, 75.5) years] were induced with pentobarbital coma median 11 (IQR 3, 33) days after seizure onset for a median of 9 (IQR 3.5, 45.4) days. A total of four to eight concurrent antiepileptics were tried prior to the pentobarbital coma. Phenobarbital, due to recurrence of seizures on weaning pentobarbital coma, was required in seven patients. Observed complications included peripheral neuropathy (77.8%), cerebral atrophy (33.3%), volume overload (44.4%), renal/metabolic (77.8%), gastrointestinal (66.6%), endocrine (55.6%), cardiac/hemodynamic/vascular (77.8%), respiratory (100%), and infectious (77.8%). The number of complications trended with duration of induced coma but was nonsignificant. Median ICU length of stay was 40 (IQR 28, 97.5) days. Overall, five patients were able to follow commands after a median 37 (IQR 25.5, 90) days from coma onset. There were eight patients that were discharged from hospital with three remaining in a prolonged unresponsive state. There was one patient that died prior to discharge.

Conclusions: This study highlights the high morbidity in patients with refractory status epilepticus requiring pentobarbital coma. Anticipating and addressing the indirect and direct complications in prolonged pentobarbital coma may improve survival and functional outcomes in patients with refractory status epilepticus.

Keywords: cerebral atrophy, pentobarbital coma, refractory status epilepticus

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Introduction

Status epilepticus is a commonly encountered neurological emergency with significant morbidity and mortality [Lowenstein and Alldredge, 1998; Pugin *et al.* 2014; Legriel *et al.* 2010]. It is initially treated with benzodiazepines and one or more antiepileptic drugs. Seizures persisting despite these measures are termed refractory status epilepticus, which occurs in 23–43% of cases [Novy *et al.* 2010]. Once status epilepticus is refractory, induction with deep sedation with intravenous pentobarbital is acceptable [Pugin *et al.* 2014]. Unfortunately, high doses of barbiturates have adverse effects that may limit their use, particularly if needed for prolonged period [Schalen *et al.* 1992a, 1992b; Claassen *et al.* 2002; Stover and Stocker, 1998; Pugin *et al.* 2014; Yaffe and Lowenstein, 1993]. Recognizing and addressing direct and indirect adverse effects may improve good outcomes from pentobarbital

coma. This retrospective review of consecutive critically ill patients with refractory status epilepticus aims to identify observed direct and indirect medical and surgical complications that occur during pentobarbital-induced coma. This study highlights the ability to use pentobarbital for a prolonged period.

Methods

We retrospectively reviewed the electronic medical records over a 1-year period at a large tertiary referral center for adult cases (i.e. ⩾18 years of age) of refractory status epilepticus treated with pentobarbital coma. The institutional review board approved this study.

Patient management

Continuous electroencephalography (CEEG) was recorded using 21 electrodes placed according to the International 10–20 System by certified EEG technologists and interpreted by board-certified electroencephalographers. CEEG seizures were defined as evolving rhythms in frequency, distribution, or morphology at ⩾2 Hertz (Hz) for ⩾10 seconds duration. Status epilepticus was classified as being convulsive (continued seizure activity for ⩾5 minutes or multiple seizures without return of consciousness) or nonconvulsive (continuous ictal pattern lasting >30 minutes or ictal pattern present in >50% of 1 hour of CEEG). Refractory status epilepticus was defined as continuous seizure activity, clinically or electrographically, despite treatment with a minimum of two antiepileptics. Withdrawal seizures were defined as occurring within 48 hours of weaning pentobarbital coma. Patients were treated for status epilepticus at the discretion of the treating physician following proposed algorithms using a benzodiazepine followed by anticonvulsant(s) (Lowenstein and Alldredge, 1998). Refractory status epilepticus was treated with pentobarbital. Pentobarbital is an anesthetic composed of 50 mg pentobarbital sodium in a propylene glycol vehicle (40%), alcohol (10%) and water to volume with an adjusted pH of 9.5.

Data acquisition

Electronic medical records were reviewed for patient demographic data, past medical history/prior history of epilepsy, status epilepticus etiology, inpatient medications, discharge data, and medical and surgical complications that occurred while in pentobarbital coma. Complications were identified by the following systems: neurological (peripheral neuropathy, cerebral atrophy on serial neuroimaging), respiratory (prolonged ventilation, chest tube, pulmonary embolus, requiring tracheostomy/percutaneous endoscopic gastrostomy), electrolytes (lactic acidosis), head/ears/eyes/nose/throat (HEENT)/skin (anasarca/tongue swelling/penile swelling, exposure keratoconjunctivitis), vascular [deep vein thrombosis (DVT)], cardiac (myocardial dysfunction, hypotension requiring pressor), endocrine (adrenal insufficiency, hypothermia, hypothyroidism), gastrointestinal [ileus, requiring total parenteral nutrition (TPN)], transaminitis [i.e. twice upper limit of normal for aspartate transaminase (AST) and alanine transaminase (ALT)], infectious [yeast in urine/lungs, sepsis, pneumonia, urinary tract infection (UTI)], and renal [acute renal failure, requiring continuous veno–veno hemodialysis (CVVHD)]. This study was approved by the institutional review board.

Data analysis

Data were analyzed with descriptive statistics. Linear regression was used to analyze the complication rate and time in pentobarbital coma. Statistics were performed with GraphPad InStat version 3.00 for Windows 95 (GraphPad Software, San Diego, CA, USA).

Review of literature

A review of the published, English literature was performed through MEDLINE using text words or medical subject headings containing 'pentobarbital status epilepticus', 'pentobarbital complication', 'pentobarbital safety', and 'refractory status epilepticus'. We excluded manuscripts that were individual case reports, pediatrics, animal studies, review articles, guidelines, and surveys. Extracted data included number of patients, duration of pentobarbital coma, complications (cardiac, respiratory, infectious, and other), and mortality.

Results

Patient characteristics

Overall, nine patients with a median age 46.4 [interquartile range (IQR) 21.7, 75.5] years were identified as having refractory status epilepticus (Table 1). The etiologies for the underlying

Table 1. Patient characteristics.

No.	Age (yrs)	Etiology	Duration of seizure prior to coma (days)	Outcome
1	80.2	Remote CVA	9	LTAC
2	21.0	Viral Enceph	2	LTAC
3	55.0	Liver failure	45	Expired
4	42.9	Midbrain lesion	78	SNF
5	85.7	HIE	2	LTAC
6	70.8	Meningioma	11	LTAC
7	19.1	Cryptogenic	11	LTAC
8	46.4	Febrile sz/HS	4	LTAC
9	22.4	NMDA LE	21	LTAC
Median (IQR)	**46.4 (21.7, 75.5)**		**11 (3, 33)**	

CVA, cerebrovascular accident; HIE, hypoxic ischemic encephalopathy; HS, hippocampal sclerosis; IQR, interquartile range; LTAC, long-term acute care; NMDA, ; LE, limbic encephalitis; SNF, skilled nursing facility; sz, seizure.

seizures included remote stroke, viral encephalitis, hypoxic ischemic encephalopathy, liver failure, meningioma, N-methyl-D-aspartate (NMDA) limbic encephalitis, midbrain structural lesion from prior surgery, and medically refractory epilepsy in two (patients: cryptogenic and febrile seizure with hippocampal sclerosis).

Anticonvulsant treatment

Overall, 4–8 antiepileptics were tried prior to the start of the pentobarbital coma (Table 2). All patients were induced in a pentobarbital coma [median bolus 10 (IQR 5, 10) mg/kg; median maintenance of 3 (IQR 1.5, 3.5) mg/kg/hr] with an aim to burst suppression at a rate of 1–2 bursts every 10 seconds. Pentobarbital coma was initiated a median of 11 days (IQR 3, 33) after seizure onset. There was one patient that required midazolam infusion after pentobarbital secondary to a nationwide shortage of pentobarbital. Pentobarbital coma was maintained for a median of 9 (IQR 3.5, 45.5) days with a maximum of 105 days. Overall, seven of the nine patients needed institution of phenobarbital due to failure to successfully wean pentobarbital coma (i.e. withdrawal seizures).

Safety

The indirectly or directly observed medical and surgical complications observed in patients in pentobarbital coma included peripheral neuropathy ($n = 7$), volume overload (pleural effusions requiring chest tubes, $n = 2$; anasarca, $n = 3$; and massive tongue swelling, $n = 3$), renal/metabolic (hemodialysis, $n = 4$; lactic acidosis, $n = 7$, with a propylene glycol level of 58mg/dl; none had other significant electrolyte disturbance), gastrointestinal (ileus, $n = 5$; diverting colostomy for sacral ulcer, $n = 1$; significant transaminitis, $n = 3$), endocrine (adrenal insufficiency, $n = 2$; persistent hypothermia, $n = 3$; thyroid function abnormalities, $n = 1$), cardiac/hemodynamic/vascular (hypotension requiring pressors, $n = 7$; cardiomyopathy with myocardial dysfunction/heart failure defined by ejection fraction (EF) $< 40\%$ or prolonged corrected QT cardiac interval (i.e. QTc) > 520 ms, $n = 2$; DVT, $n = 2$; pulmonary embolism, $n = 1$), respiratory (need for prolonged mechanical ventilation, $n = 9$, of which 6 required ventilation > 30 days; tracheostomy and gastrostomy, $n = 7$), and infections from various sources ($n = 7$, with 1 developing septic shock). Median intensive care unit (ICU) length of stay was 40 (IQR 28, 97.5) days. There were three patients that had cerebral atrophy seen on follow-up brain magnetic resonance imaging (MRI). These three patients were placed in a pentobarbital coma median 11 (range 2–21) days after seizure onset and maintained in burst suppression for a median of 62 (range 29–105) days. Initial brain MRI [performed median 12 (range 1–14) days after seizure onset] did not show cerebral atrophy. Subsequent imaging [median 53 (IQR 23, 93) days from seizure onset] showed persistent generalized cerebral atrophy (Figure 1). Table 3 summarizes the medical and surgical complications observed in patients with refractory status epilepticus maintained in a pentobarbital coma. The absolute number of complications positively trended with duration of induced coma, but was nonsignificant ($p = 0.24$; Figure 2).

Table 2. Sequential therapies provided for treatment of refractory status epilepticus.

		Patient								
		1	2	3	4	5	6	7	8	9
Antiepileptic	**1st**	PHT	PHT	PHT	PHT	LEV	PHT	PHT	ZON	PHT
	2nd	VPA	LEV	LEV	ZON	Propofol	LTG	VPA	Primidone	Propofol
	3rd	MDZ	VPA	LCM	LCM	LZM	LCM	Propofol	VPA	LCM
	4th	LEV	Propofol	Propofol	LEV	LCM	PGB	LV	LEV	LEV
	5th	LCM	LCM	PB	KLO	PHT	VPA	PB	MDZ	MDZ
	6th	PB	MDZ		PHB	PB	PHT	LCM	PB	PB
	7th	PHB	PB		PB		LEV	TPM	LCM	PHB
	8th		PHB				Propofol	Ketogenic diet	PHB	FBM
	9th		FBM				PB	PHB		MDZ
	10th						PHB	FBM		

FBM, felbamate; KLO, klonopin; LCM, lacosamide; LEV, levetiracetam; LZM, lorazepam injection; MDZ, midazolam infusion; PB, pentobarbital infusion; PGB, pregabalin; PHB, phenobarbital; PHT, phenytoin; Propofol, propofol infusion; VPA, valproic acid; ZON, zonegran.

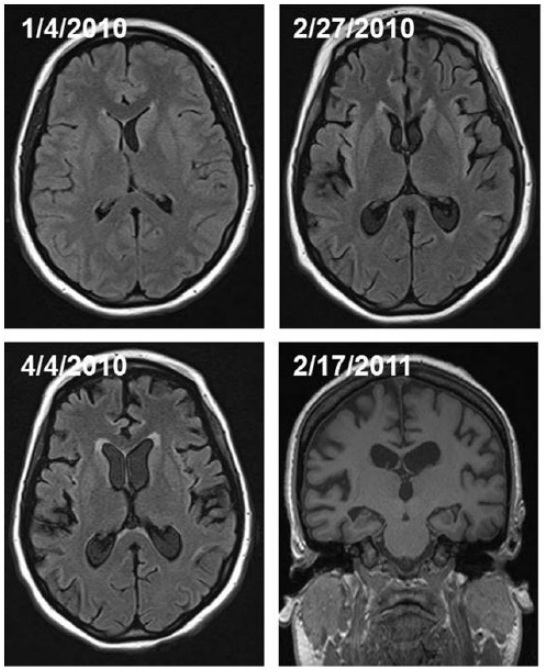

Figure 1. Fluid attenuated inversion recovery sequences (FLAIR) from brain magnetic resonance imaging (MRI) illustrating the persistent cerebral atrophy observed in a patient in a prolonged pentobarbital coma.

Outcome

Overall, one (11.1%) patient died within 24 hours of initiating coma due to fulminant liver failure from another etiology. There were three (33.3%) patients that stayed in a persistent state of unresponsiveness after the induced coma (range 136–306 days). Overall, five (55.6%) patients recovered consciousness and regained ability to follow commands after a median of 37 (IQR 25.5, 90) days from coma onset. Of those discharged, six (66.7%) were discharged to long term acute care (LTAC), one (11.1%) to a subacute nursing facility (SNF), and one (11.1%) transferred to another hospital where she died 15 days after discharge (Table 1).

Literature review

A total of 46 articles were identified through database searching. Overall, 41 articles were excluded. The excluded articles were case reports (n = 9), pediatric articles (n = 10), animal articles (n = 3), review articles (n = 16), guidelines (n = 2), and a survey (n = 1). The five included articles have 73 total patients. Mean ± standard deviation duration of anesthesia was 69.2 ± 47.3 hrs. The most commonly observed complication was respiratory failure with need for mechanical ventilation (100%) followed by hypotension/cardiac complications (79.3%). The mortality ranged from 11.8% to 77% (Table 4).

Discussion

Our study highlights the high morbidity of patients with refractory status epilepticus treated with pentobarbital coma. It also highlights the ability to safely use pentobarbital for extended amounts of time. This study was not intended to infer a direct causality of barbiturate coma to complications. Rather, it highlights direct and indirect complications that were observed in critically ill patients treated

Table 3. Observed direct and indirect medical and surgical complications in patients maintained in a pentobarbital coma for refractory status epilepticus.

	Patient									Total	%
	1	2	3	4	5	6	7	8	9		
ICU length of stay, days	39	143	6	17	40	40	80	61	115		
Length of pentobarb coma, days	4	29	1	5	3	9	62	20	105		
Neurological											
Peripheral neuropathy	*	*			*	*	*	*	*	**7**	**77.8**
Cerebral Atrophy		*					*		*	**3**	**33.3**
Respiratory											
Trach/PEG	*	*			*	*	*	*	*	**7**	**77.8**
Ventilator > 30 days	*	*			*		*	*	*	**6**	**66.7**
Chest tube							*	*		**2**	**22.2**
Pulmonary embolus									*	**1**	**11.1**
Electrolyte Abnormality											
Lactic acidosis		*	*		*	*	*	*	*	**7**	**77.8**
HEENT/Skin											
Anasarca	*					*	*			**3**	**33.3**
Tonge swelling						*	*	*		**3**	**33.3**
Penile edema						*				**1**	**11.1**
Exposure keratoconjunctivitis						*	*	*		**3**	**33.3**
Vascular											
DVT						*			*	**2**	**22.2**
Cardiology											
Myocardial Dysfunction							*	*		**2**	**22.2**
Hypotension	*		*		*	*	*	*	*	**7**	**77.8**
Endocrine											
Adrenal insufficiency							*	*		**2**	**22.2**
Hypothermia	*				*		*			**3**	**33.3**
Hypothyroidism									*	**1**	**11.1**
Gasroenterology											
Ileus	*	*					*	*	*	**5**	**55.6**
TPN		*					*			**2**	**22.2**
Transaminitis		*			*		*			**3**	**33.3**
Infectious Disease											
Yeast in urine/lungs	*	*					*	*		**4**	**44.4**
Sepsis								*		**1**	**11.1**
PNA		*	*		*			*		**4**	**44.4**
UTI	*					*	*	*		**4**	**44.4**
Renal											
CVVHD			*		*		*			**3**	**33.3**
Acute renal failure					*					**1**	**11.1**
Sum	**9**	**10**	**4**	**0**	**10**	**10**	**19**	**15**	**10**		

CVVHD, continuous veno-veno hemodialysis; DVT, deep venous thrombosis; HEENT, head/ears/eyes/nose/throat; PEG, percutaneous endoscopic gastrostomy; PNA, pneumonia; TPN, total parenteral nutrition; UTI, urinary tract infection.

with a prolonged duration of pentobarbital coma. Recognizing potential medical and surgical complications in patients with refractory status epilepticus requiring barbiturate coma may lead to improved outcomes [Wittman and Hirsch, 2005; Young *et al.* 1996].

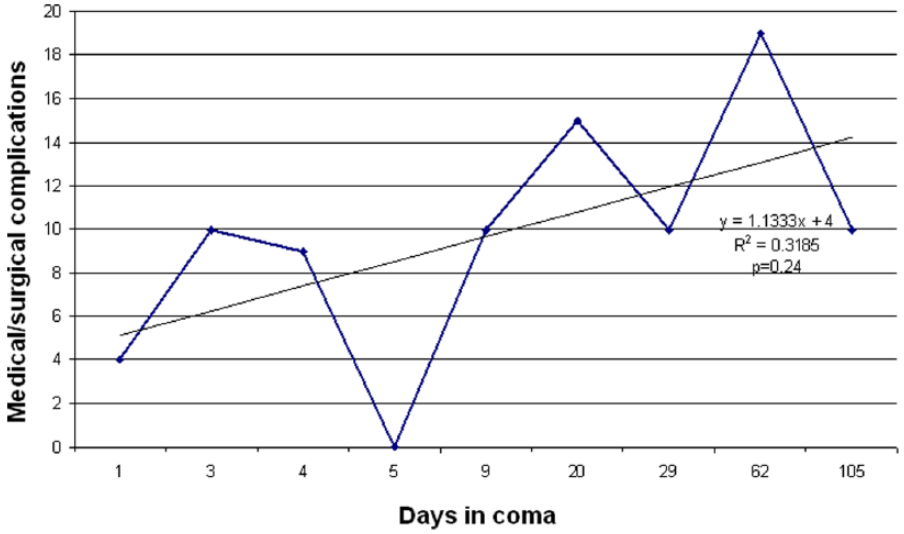

Figure 2. Graphical representation illustrating the trend of absolute number of medical and surgical complications with respect to duration of pentobarbital coma.

A total of seven patients had an infection from various sources. Increased propensity to infection may be related to the immunosuppressant effects of pentobarbital coma [Schmutzhard and Pfausler, 2011]. Barbiturates cause immunosuppression by reduction of phagocytic activity of leukocytes, decreasing activation of peripheral lymphocytes, and depression of chemotactic migration of white blood cells [Parviainen *et al.* 2007; Neuwelt *et al.* 1982; Kress *et al.* 1989; Kress and Segmuller, 1987]. Immunosuppression increases the risk of line-associated infections and ventilator-associated pneumonia. Pentobarbital also reduces gastric motility putting a patient at potential risk for transmural translocation of intestinal bacteria and sepsis from intestinal organisms [Schmutzhard and Pfausler, 2011]. Altered gastric motility also makes absorption of orally-available antiepileptics less reliable and compromises nutritional status. We also observed hemodynamic instability and myocardial dysfunctions (i.e. heart failure and prolongation of QTc) resulting in hypotension and volume overload [Schmutzhard and Pfausler, 2011; Ji *et al.* 2009; Claassen *et al.* 2001, 2002]. Patients in pentobarbital coma have longer mechanical ventilation times and require aggressive venous thrombosis prophylaxis due to prolong immobility. Indeed, two patients in our study developed DVTs and one with a pulmonary embolus. It has been suggested that since barbiturates redistributes in tissue in a nonlinear fashion after prolonged use, accumulation occurs leading to prolonged recovery [Parviainen *et al.* 2007]. Pentobarbital coma also is known to either contribute directly to the development of a peripheral polyneuropathy or its development may be a manifestation of prolonged critical illness [Hermans *et al.* 2008; Stevens *et al.* 2007]. Overall, seven of our patients had had clinical signs of polyneuropathy and myopathy with one having an electromyography (EMG) / nerve conduction study (NCS) verifying the clinical suspicion.

Lactic acidosis is also encountered in prolonged pentobarbital comas [Ji *et al.* 2009; Miller *et al.* 2008]. This may be secondary to the propylene glycol base (40% by volume) used with pentobarbital [Ji *et al.* 2009]. Propylene glycol is predominantly metabolized in the liver to lactate, acetate, and pyruvate with the remainder excreted unchanged through the kidney [Bledsoe and Kramer, 2008]. A total of seven patients in our series had prolonged lactic acidosis (median 9 days). Overall, one patient had a propylene glycol level of 58 mg/dl with no associated renal failure (Bledsoe and Kramer, 2008). It has been suggested that propylene glycol decreases renal clearance by saturating the proximal tubule [Speth *et al.* 1987; Zar *et al.* 2007]. A propylene glycol level was available only in one patient, but four other patients required hemodialysis for acute renal failure with metabolic abnormalities or volume overload.

Generalized cerebral atrophy was seen in 33% of our patients. The progression of cerebral atrophy in patients with refractory status epilepticus is unclear. It may be a reflection of the etiology causing the

Table 4. Systematic review of literature of observed complications and outcomes in pentobarbital coma for refractory status epilepticus.

Author, Year	Design	Total number of patients	Duration of anesthesia (hrs)	Hypotension/ cardiac complications	Mechanical ventilation/ respiratory complications	Infectious complications	Other complications	Mortality
Rashkin *et al.* 1987	Retrospective observation	9	31.6	100.0%	NA	NA	NA	77.0%
Lowenstein *et al.* 1987	Retrospective Observation (*n=8*); prospective (*n=6*)	14	62.6	64.3%	100.0%	7.1%	87.5% (cognitive); 7.1% (renal); 14.3% (neuropathy)	42.9%
Osorio and Reed, 1989	Retrospective Observation	12	80.6	100.0%	100% (16.7% unable to wean)	66.7%	16.7% (anemia), 100.0% (constellation of weakness, confusion, ataxia, visual disturbance)	11.8%
Van Ness, 1990	Retrospective observation	7	27.1	100.0%	100.0%	NA	NA	42.9%
Pugin *et al.* 2014	Retrospective observation	31	144	32.0%	100.0%	45.0%	10.0% (DVT), 10.0% (ileus), 3.2% (peripheral neuropathy)	42.0%

DVT, deep vein thrombosis; NA, not applicable.

refractory status epilepticus or the status epilepticus itself with its subsequent treatment and critical illnesses. Cross-sectional studies of this phenomenon are complicated by the possibility of cortical damage from the initial ictal insult, nonlesional MRI, possibility of cerebral atrophy from prolonged critical illness and associated multisystem/metabolic abnormalities, and effects of prolonged high dose multi-antiepileptic therapy [DeGiorgio *et al.* 1999]. It has been proposed that prolonged sedation with anesthetics disrupts the ascending reticular activating system allowing for decoupling from the posterior parietal cortex, medial temporal lobe, and prefrontal cortex [Gunther *et al.* 2007]. This prolonged decoupling may lead to excitotoxicity and ultimately apoptosis [Gunther *et al.* 2007]. This could be one hypothesis to explain the cerebral atrophy. This hypothesis further highlights the urgency of aggressive intervention in patients who present with status epilepticus.

There is considerable amount of controversy on the use of continuous infusion of intravenous antiepileptics for treating refractory status epilepticus. Controversy exists as to the most efficacious agent to use, preference of high monotherapy over combination antiepileptics, therapeutic dose ranges, duration of coma, depth of coma, thresholds for treating abnormal rhythms on EEG, and how continuous should the electroencephalography monitoring be [Corry *et al.* 2008; Rossetti and Lowenstein, 2011; Jordan and Hirsch, 2006]. A systematic review of the literature by Claasen and colleagues showed that outcomes of patients in status epilepticus are poor [Claassen *et al.* 2002]. Additionally, there is no difference in outcome on choice of antiepileptic or titration goal [Claassen *et al.* 2002]. However, they did find that pentobarbital coma is associated with less short-term treatment failure, breakthrough seizures, and the need to switch to another antiepileptic [Claassen *et al.* 2002]. However, the use of pentobarbital coma has significant morbidity and mortality [Rashkin *et al.* 1987; Lowenstein *et al*. 1988; Osorio and Reed, 1989; Van Ness, 1990; Pugin *et al.* 2014]. We did not analyze comparative efficacy of various antiepileptic therapies for refractory status epilepticus. Overall, four of our nine patients needed further addition of antiepileptics (other than phenobarbital) after instituting the pentobarbital coma. Only one patient required a midazolam infusion.

In conclusion, this study highlights the observed complications of prolonged pentobarbital coma for treatment of refractory status epilepticus in critically ill patients from a single center. It also highlights the ability to safely use prolonged pentobarbital coma in critically ill patients. Anticipating and addressing complications in prolonged pentobarbital coma, whether directly or indirectly related to the coma or critical illness, can improve survival and functional outcomes in patients with medically refractory status epilepticus. A prospective study comparing continuous infusions of anticonvulsants (i.e. pentobarbital, midazolam, and propofol) in comparison to combination multi-antiepileptic agents is necessary to determine what strategies can improve outcomes in the critically ill patients with refractory status epilepticus with minimal systemic complications.

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