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ORIGINAL ARTICLE

Electroconvulsive Therapy for Refractory Status Epilepticus: A Case Series

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Abstract
Background Status epilepticus refractory to conventional anti-epileptic drugs typically has a poor prognosis, but patients may recover well if seizures can be stopped. Case reports suggest that electroconvulsive therapy (ECT) may stop seizures in patients with refractory status epilepticus, and we sought to examine its effectiveness in a series of patients.
Methods Three consecutive patients with refractory status epilepticus at our institution were treated with ECT after other therapies had failed.
Results ECT stopped seizures in 2 of 3 patients. One patient had complete neurological recovery; the other was left with mild cognitive impairment and epilepsy, but returned to independent living.
Conclusion ECT may be an effective therapy for refractory status epilepticus and warrants further study for this indication.

Keywords Status epilepticus · Electroconvulsive therapy · Anticonvulsants

Authors' Contributions HK collected clinical data and prepared the first draft of the manuscript. SBC collected EEG data, drafted the description of EEG results, and edited the manuscript. MH assisted with the first draft and provided significant editing of the manuscript. SEH collected ECT data, drafted the description of ECT procedures, and edited the manuscript. SAJ was responsible for the study inception, overall design, and manuscript editing.

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Introduction

Status epilepticus is a potentially devastating medical emergency that affects 60,000–120,000 Americans per year [1]. It is classically defined as a seizure that lasts more than 30 min, or repeated seizures that prevent the patient from regaining full consciousness [2]. Thus defined, its mortality is approximately 25%, compared to less than 5% from seizures shorter than 30 min. Its treatment is particularly relevant to the neurocritical care community, because it often requires prolonged use of anesthetic agents in an intensive care unit (ICU) [3].

Most patients with status epilepticus are successfully treated with benzodiazepines and conventional anti-epileptic drugs such as phenytoin, but some require anesthetic agents such as propofol, midazolam, or pentobarbital to suppress seizures [3, 4]. This requires endotracheal intubation, admission to an ICU, and continuous electroencephalographic (EEG) monitoring. Anesthetic agents are important in preventing cortical damage from sustained seizures [5], but eventually other means of seizure control are needed, so high doses of multiple conventional anti-epileptic drugs are given and anesthetics are weaned. In some patients this fails, leading to so-called refractory status epilepticus, defined as ongoing seizures in the face of multiple anti-epileptic medications [6, 7].

Refractory status epilepticus carries a grim prognosis [8]. Patients with uncontrolled seizures often succumb to complications of prolonged anesthesia and critical illness or the toxicity of anti-epileptic drugs [6]. However, remarkable recovery may occur if seizures are stopped, especially in cases without significant underlying brain damage [8]. Therefore, alternative methods of stopping seizures are crucial when conventional anti-epileptic drugs fail. One such method is electroconvulsive therapy (ECT),

Table 1 Pertinent results of diagnostic investigations

	Case 1	Case 2	Case 3
CSF profile	Normal	225 WBC	6 WBC
		Mostly lymphocytes	Mostly lymphocytes
MRI results	Initially: normal	Normal	T2 prolongation and reduced diffusion in the left claustrum and superior frontal gyrus
	After 6 weeks: scattered areas of sub-cortical and thalamic T2 prolongation		
Tests for infection (all negative)	PCR of CSF for HSV, VZV, CMV, HHV-6	PCR of CSF for HSV, VZV, CMV, HHV-6	PCR of CSF for HSV, VZV, CMV, HHV-6
	Bacterial and fungal cultures of CSF	Bacterial and fungal cultures of CSF	Bacterial and fungal cultures of CSF
Markers of auto-immunity (all negative)	ANA, RF, Sjogren's antibodies, VGKC antibody	ANA, RF, Sjogren's antibodies, VGKC antibody	ANA, RF, Sjogren's antibodies, VGKC antibody

CSF cerebrospinal fluid, *MRI* magnetic resonance imaging, *WBC* white blood cells, *PCR* polymerase chain reaction, *HSV* Herpes simplex virus, *VZV* varicella zoster virus, *CMV* cytomegalovirus, *HHV-6* human herpes virus 6, *ANA* anti-nuclear antigen, *RF* rheumatoid factor, *VGKC* voltage-gated potassium channel

which case reports suggest may effectively treat refractory status epilepticus [9–13], possibly by inducing endogenous anti-convulsant pathways [14, 15]. We report here the effect of ECT on three consecutive patients with refractory status epilepticus treated at our institution. The patients' surrogates provided informed consent for ECT, which was administered in accordance with federal and state laws. This case series was certified as exempt from review by our institutional ethics committee.

Case One

A previously healthy 32-year-old woman was admitted to another hospital with fever, headache, and seizures. Intravenous acyclovir was given for possible viral encephalitis, but she developed refractory status epilepticus. One week later, computed tomography (CT) of her brain revealed diffuse cerebral edema, and she was transferred to our Neuroscience ICU for further management. Extensive

Table 2 Therapies used in an attempt to stop seizures

	Medication	Dose	Days of illness
Case 1	Valproate sodium	Titrated to high therapeutic level	1–10, 19–40
	Phenytoin	Titrated to high therapeutic level	10–19
	Phenobarbital	Titrated to high therapeutic level	1–10, 35-discharge
	Levetiracetam	2000 mg bid	1–35
	Topiramate	200 mg qid	1–35
	Pentobarbital	Titrated to suppression of EEG	14–17
	Ketamine	0.5 mg/min	30–31
	ECT	See Table 3	30–34
Case 2	Phenytoin	Titrated to high therapeutic level	1-death
	Levetiracetam	2000 mg bid	15-death
	Valproate sodium	Titrated to high therapeutic level	20-death
	Pentobarbital	Titrated to suppression of EEG	16–17, 27–28, 32–38
	Ketamine	0.5 mg/min	21–22
	ECT	See Table 3	30–33
Case 3	Phenytoin	Titrated to high therapeutic level	1-discharge
	Valproate sodium	Titrated to high therapeutic level	1-discharge
	Pentobarbital	Titrated to suppression of EEG	Not recorded
	Levetiracetam	1500 mg bid	Not recorded
	Topiramate	200 mg bid	26-discharge
	Phenobarbital	Titrated to high therapeutic level	35-discharge
	Isoflurane	Not recorded	40
	Ketamine	Not recorded	42
	ECT	See Table 3	70–90

ECT electroconvulsive therapy, *EEG* electroencephalogram

diagnostic evaluation did not reveal an etiology, although infectious encephalitis was considered most likely (Table 1). Despite high doses of multiple anti-epileptic drugs (Table 2), EEG monitoring revealed refractory status epilepticus whenever propofol and midazolam were weaned (Fig. 1). High doses of methylprednisolone were given for possible autoimmune encephalitis, with no abatement of seizures. Three successive trials of pentobarbital to achieve complete suppression of the EEG for 72 h resulted in no improvement. A trial of ketamine also failed to control her seizures. Six weeks into her illness, we weaned all anti-epileptic drugs and performed 4 cycles of ECT over a period of 5 days (Table 3). Propofol and midazolam were given between treatments to maintain burst-suppression on the EEG. ECT was administered via bifrontotemporal leads with a Somatics Thymatron System IV device (Somatics, LLC, Lake Bluff, IL, USA) programmed to deliver a pulse width of 0.5 ms, at the longest stimulus duration available to achieve the standard maximum output of 504 mC. Continuous EEG monitoring was used to ensure that the ECT was provoking generalized electrographic seizures (Fig. 1). Rocuronium was used for paralysis to avoid succinylcholine in a debilitated patient. On each day of therapy, at least three electrical stimuli

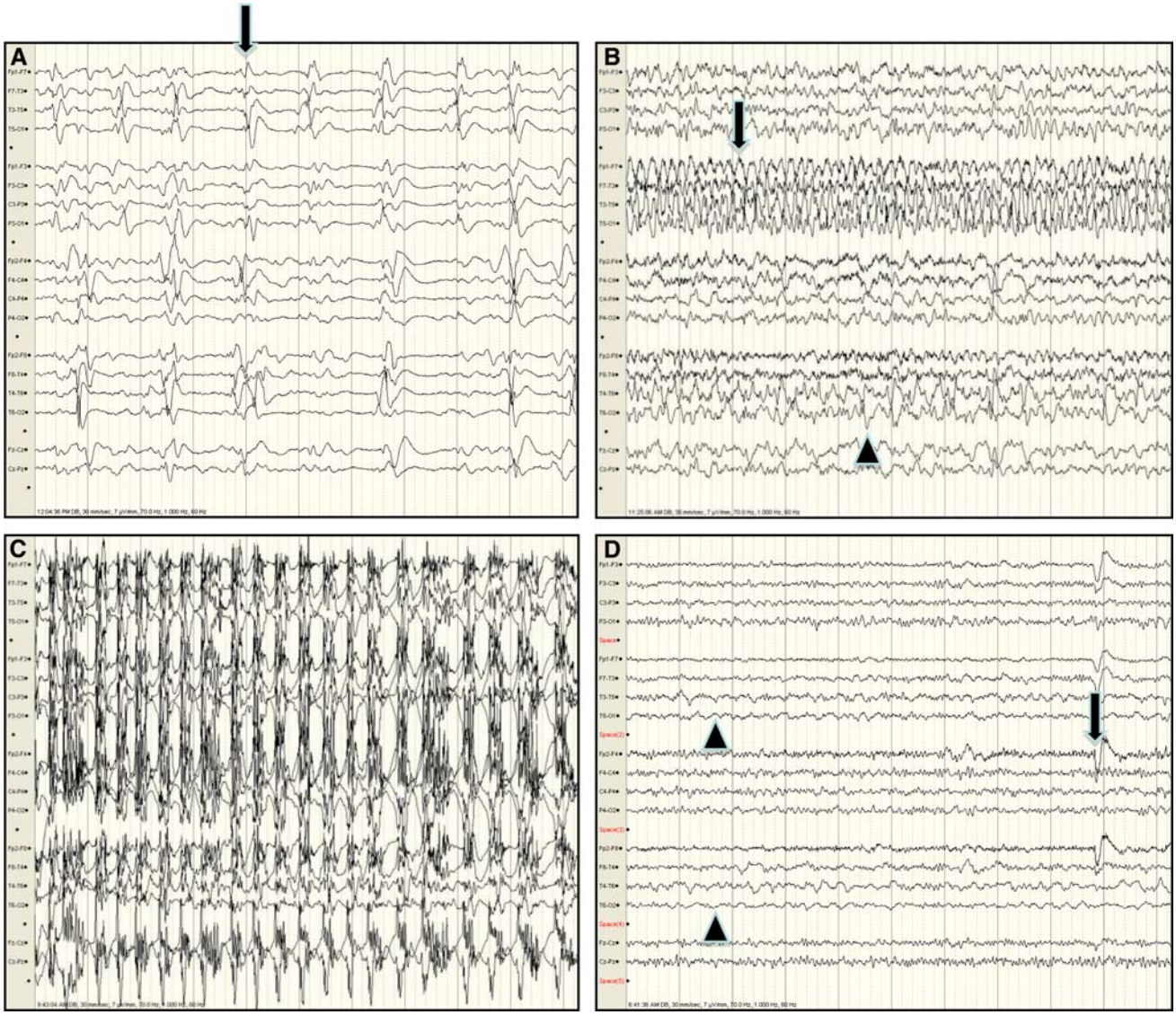

Fig. 1 Samples of electroencephalograms from case 1. Displayed are four electroencephalograms in longitudinal bipolar montage showing (**a**) bilateral periodic lateralized epileptiform discharges (PLEDs) prior to electroconvulsive therapy (ECT), **b** a focal left posterotemporal seizure (*arrow*) with concurrent right posterotemporal PLEDs (*arrowhead*) prior to ECT, **c** a generalized seizure associated with ECT, and **d** the background roughly 1 week following ECT demonstrating the return of some anteroposterior organization with resolution of PLEDs, new blink artifact (*arrow*), and persistent slowing in the region of prior epileptiform activity (*arrowheads*)

Table 3 Details of electroconvulsive therapy used in case 1

Day	Time	Current (A)	Frequency (Hz)	Pulse width (ms)	Duration (s)	Energy (mC)	Seizure duration (s)
1	08:32	0.91	70	0.5	8.0	508.4	19
	08:35	0.91	70	0.5	8.0	509.0	20
	08:40	0.91	70	0.5	8.0	510.2	25
2	09:15	0.90	70	0.5	8.0	506.0	30
	09:19	0.91	70	0.5	8.0	507.0	27
	09:23	0.91	70	0.5	8.0	507.4	31
	09:28	0.91	70	0.5	8.0	507.9	37
3	09:16	0.90	70	0.5	8.0	506.3	33
	09:20	0.90	70	0.5	8.0	506.4	32
	09:24	0.90	70	0.5	8.0	506.5	35
4							
5	09:41	0.90	70	0.5	8.0	504.6	37
	09:45	0.90	70	0.5	8.0	505.7	57
	09:51	0.90	70	0.5	8.0	506.5	65

were administered in succession. After the last round of ECT, the EEG showed that the patient's seizures had resolved (Fig. 1), and she began to regain consciousness. Over several weeks, she became more conversant and interactive, and was discharged to an acute rehabilitation facility. Two months after discharge, she was seen in our clinic; she complained of retrograde amnesia for the months prior to her illness and anterograde amnesia for the duration of her stay in the ICU, but otherwise felt well. She scored 30 out of 30 on her Mini-Mental State Examination and had a normal neurological examination.

Case Two

A previously healthy 41-year-old woman developed fever, headache, and changes in her personality. Cerebrospinal fluid (CSF) analysis at an outside hospital revealed a moderate pleocytosis (Table 1), and she was treated with intravenous acyclovir for viral encephalitis. Fosphenytoin was started after a seizure, but she continued to have seizures and a decline in her mental status. Two weeks after her symptoms began, she was transferred to our Neuroscience ICU for management of refractory status epilepticus. Laboratory studies did not reveal the cause of her encephalitis, and an MRI study of the brain was normal (Table 1). Despite receiving high doses of multiple anti-epileptic drugs (Table 2), she continued to have electrographic seizures whenever anesthetic agents were weaned. A trial of ketamine was unsuccessful. She underwent four daily cycles of ECT using a protocol similar to that described in case 1, but her seizures continued, so she was given pentobarbital to achieve complete suppression of the EEG. After several days of pentobarbital infusion, she developed multiple complications, including multi-drug resistant nosocomial pneumonia and acute renal failure. At the request of her family, life support was withdrawn, and the patient died. Pathologic examination of the brain revealed an active inflammatory infiltrate consistent with ongoing meningoencephalitis; no organism was identified.

Case Three

A previously healthy 26-year-old woman experienced seizures after several days of flu-like symptoms. Analysis of her CSF at another hospital showed a mild pleocytosis (Table 1). Intravenous acyclovir and phenytoin were administered, but she continued to have seizures. One week into her course, she was transferred to our Neuroscience ICU for further management. An MRI revealed abnormal T2 prolongation and reduced diffusion in the left claustrum and superior frontal gyrus, suggesting infectious cerebritis. Laboratory testing did not reveal the etiology of her imaging findings, and she continued to receive broad-spectrum antibiotics and anti-viral drugs. Despite high doses of conventional anti-epileptic drugs, she experienced both focal and generalized electrographic seizures whenever anesthetic agents were weaned. This continued despite three trials of pentobarbital to achieve suppression of the EEG. Trials of isoflurane and ketamine were unsuccessful. High doses of methylprednisolone were given without any effect. Two months into her course, we administered ECT using a protocol similar to that in case 1. The first two cycles failed to provoke a generalized electrographic seizure, but the 3rd round succeeded after midazolam was

pharmacologically reversed. After the 4th cycle of ECT, the patient's seizures decreased in frequency but continued, so another four rounds of ECT were administered, for a total of eight cycles. During this time, she began to slowly awaken, and she was discharged to an acute rehabilitation facility 3 months after her symptoms began. She has been seen regularly in our clinic for several years. She has frequent seizures and mild difficulty with short-term memory and concentration, but she lives independently and has had no further episodes of status epilepticus.

Discussion

Status epilepticus can have multiple underlying causes. Some, such as hypoxic-ischemic brain injury, are associated with a mortality of 80% [1]. However, many etiologies of status epilepticus are much more benign, especially if they do not involve direct insults such as hypoxia or infarction [1]. If seizures can be stopped, patients in this second category can make a remarkable recovery, as demonstrated in cases 1 and 3.

Most cases of status epilepticus are not refractory to conventional treatment, but sometimes alternative methods are needed to stop seizures. In the cases described earlier, we turned to ECT after we had exhausted potent combinations of conventional anti-epileptic drugs, multiple trials of complete EEG suppression with anesthetic agents, and more infrequently used therapies such as inhaled anesthetics and ketamine. We chose ECT because experimental evidence indicates that it augments endogenous anti-convulsant neurotransmitters such as gamma-aminobutyric acid (GABA) and reduces neuronal metabolic activity [14, 15], producing a refractory period that can interrupt the continuous seizure activity seen in status epilepticus, a condition in which endogenous anti-convulsant mechanisms have failed [12]. Several case reports [9–13] (Table 4) and our experience as described earlier suggest that these theoretical anti-epileptic properties of ECT are in fact clinically effective. Furthermore, compared to other

Table 4 Summary of published case reports describing the use of electroconvulsive therapy (ECT) for status epilepticus or frequent seizures

	Clinical features	Therapies prior to ECT	Timing of ECT	Dose of ECT	Outcome
Viparelli and Viparelli [9]	A 19-year-old woman with epilepsy presented with over 40 seizures per day, without overt status epilepticus	Phenytoin and diazepam	Not reported	Two sessions over 3 days	Seizures stopped and patient returned to baseline
Carrasco Gonzalez et al. [10]	A 25-year-old man with a history of traumatic brain injury presented with status epilepticus	Phenytoin, carbamazepine, diazepam, phenobarbital, pentobarbital	40 days after onset of seizures	Six sessions over 2 weeks	Seizures stopped and patient returned to baseline
Griesemer et al. [11]	A 13-year-old boy with microgyria and epilepsy presented with frequent seizures	Phenobarbital, phenytoin, acetazolamide, clonazepam, valproate, gabapentin, lamotrigine, and felbamate	Not reported	Four sessions over 9 days	Mild improvement in seizure frequency and severity
	Same patient above presented 1 year later with nonconvulsive status epilepticus	Not reported	Not reported	Three daily sessions	Termination of status epilepticus, with significant decrease in seizure frequency over following month
	A 10-year-old girl with microcephaly and epilepsy presented with frequent seizures	Phenobarbital, phenytoin, carbamazepine, valproate, felbamate, and gabapentin	Not recorded	Six sessions over 2 weeks	Temporary decrease in seizure frequency
Lisanby et al. [12]	A 36-year-old man with epilepsy presented with status epilepticus	Phenytoin, nitrazepam, phenobarbital, vigabatrin, pentobarbital, propofol, midazolam	26 days after onset of seizures	Five daily sessions	Seizures stopped but patient remained comatose
Cline and Roos [13]	A 39-year-old previously healthy man presented with herpes simplex encephalitis and status epilepticus	Fosphenytoin, valproate, pentobarbital, levetiracetam, oxcarbazepine, topiramate, lorazepam, felbamate	103 days after onset of seizures	Three daily sessions	Termination of status epilepticus, continued episodic seizures, and significant residual neurological deficits

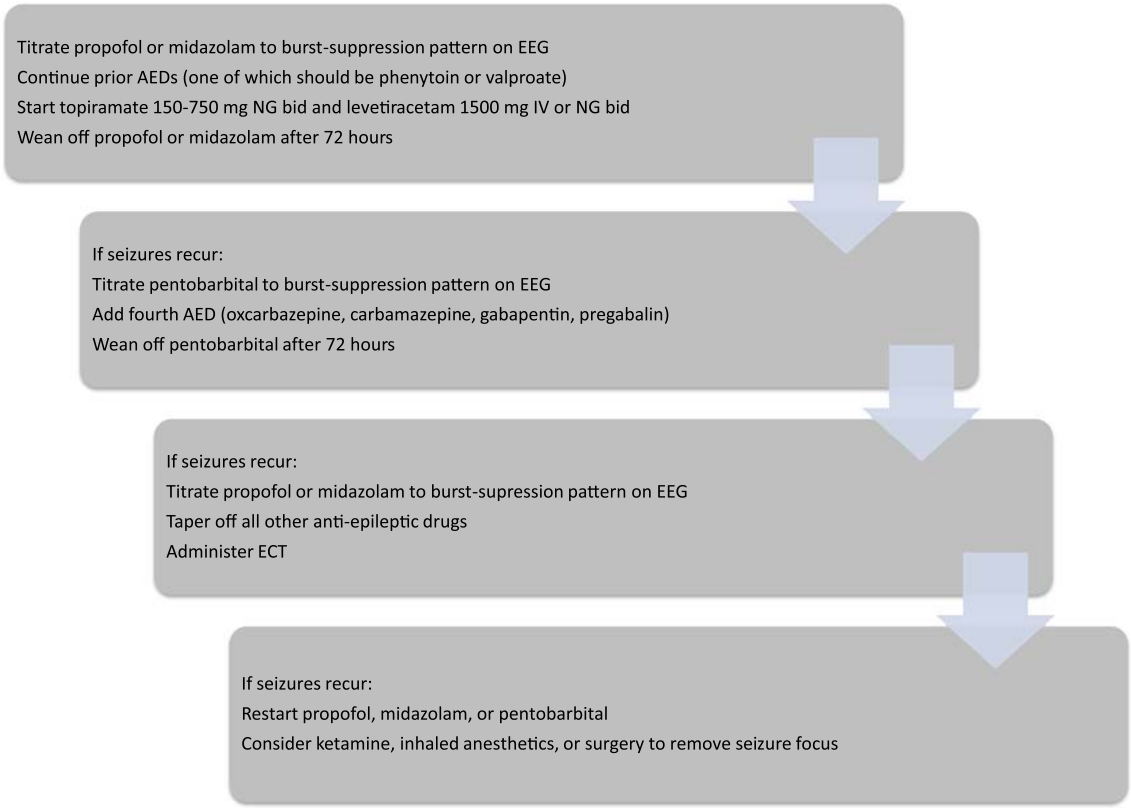

Fig. 2 Suggested algorithm for treatment of refractory status epilepticus: ongoing seizures despite high doses of at least two anti-epileptic drugs (AEDs)

treatments for refractory status epilepticus, such as prolonged barbiturate coma, ketamine, inhaled anesthetics, or surgery to excise seizure foci [8], the safety of ECT has been proven during widespread use in the treatment of psychiatric disorders [16].

In the absence of other scientifically proven therapies for refractory status epilepticus, we feel that our case series and the case reports cited above justify further use and study of ECT for this indication (Fig. 2). Based on this combined experience, a reasonable strategy would be to administer daily sessions of ECT for 3–8 days, with adjustment based on the patient's response. This recommendation should be considered in light of the limitations of our study, including its small size and lack of controls. The efficacy of ECT should be demonstrated in a larger group of patients, preferably with a control group. To be feasible, such a study may require a crossover design in which patients are treated with either standard therapy (e.g., pentobarbital infusion) or ECT, and then receive the alternative therapy if the first treatment fails. We hope that our small success in using ECT to treat refractory status epilepticus will lead to such studies, and eventually to better care for this common and potentially devastating but treatable illness.

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