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Clinical letter

# Ultra-short burst suppression as a "reset switch" for refractory status epilepticus

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Based on criteria from the Neurocritical Care Society Status Epilepticus Guideline Writing Committee, status epilepticus (SE) is defined as five or more minutes of continuous seizure activity or recurrent seizure activity without returning to baseline. Patients who fail standard antiepileptic drug (AED) regimens for SE (initial benzodiazepine plus second antiepileptic drug) are considered to be in refractory status epilepticus (RSE). RSE carries a mortality that is three-fold that of non-refractory SE [1], and occurs in 23%–43% of patients with SE [1].

Given the lack of robust clinical trials examining RSE, the management of RSE including refractory non-convulsive SE is not well defined [1]. Standard treatment regimens for RSE include repeating initial boluses of previously administered AEDs or initiating continuous infusion AEDs. These continuous infusions often take the form of general anesthetics, with the desired goal of seizure suppression or burst suppression. Burst suppression, defined as an EEG pattern with periods of high-voltage electrical activity alternating with periods of no activity, is often used as a surrogate end-point for titration of anesthetic agents. Burst suppression can provide a window of seizure control while reversible etiologies are being investigated/treated. Moreover, it may act as a theoretical "reset switch" and break the cycle of SE. Unfortunately, the optimal duration of burst suppression for RSE has not been established. Although a common practice favors burst suppression (titrated to 10 s interburst intervals) for 24–48 h to reduce the risk of subsequent relapse, there is insufficient data to suggest that short periods of burst suppression increase relapse risk. Furthermore, because of its associated toxicities, burst suppression poses significant morbidity that may be dependent on the amount of time spent in burst suppression [2]. Herein, we demonstrate that an ultra-short (< 2 h) period of burst suppression may be a viable method to control RSE and should be attempted in appropriate situations.

A 74-year-old female with a history of epilepsy (on levetiracetam), diabetes mellitus, hyperlipidemia, and hypertension presented to her local emergency department after experiencing two witnessed seizures. On arrival, the patient was somnolent, nonverbal and was not following any commands in her native language (Spanish). Her vital signs were notable for a blood pressure of 215/85, pulse of 108, temperature of 38.9 °C, saturation of 98% on room air, and respiratory rate of 18. Initial laboratory evaluation was notable for a WBC of 11.5 K/μL and glucose of 457 mg/dL. Lumbar puncture revealed RBC 39 cells/mm [3], WBC 4 cells/mm [3], protein of 32 mg/dL, and glucose of 192 mg/dL. She was started on empiric broad-spectrum antibiotics but continued to experience several seizures characterized by forced downgaze and unresponsiveness without any obvious tonic-clonic posturing. Seizures continued to persist despite levetiracetam (2000 mg/day), additional lorazepam (2 mg), and supratherapeutic levels (35.9 μg/mL) of phenytoin. Continuous EEG monitoring was performed and revealed 20 seizures/hr consistent with non-convulsive refractory status epilepticus (Fig. 1).

These seizures originated focally with rhythmic sharp and slow wave discharges occurring over the right posterior quadrant (Fig. 2A), and then generalized into 2 Hz spike and wave discharges (Fig. 2B). Because of ongoing seizures despite treatment of her febrile illness and correction of hyperglycemia, the patient was intubated and started on propofol (at an average rate of 50 mcg/kg/min). Burst suppression pattern was rapidly achieved consisting of 1–2 second bursts of theta/delta activity with intermixed sharp contours and 10 s suppressions

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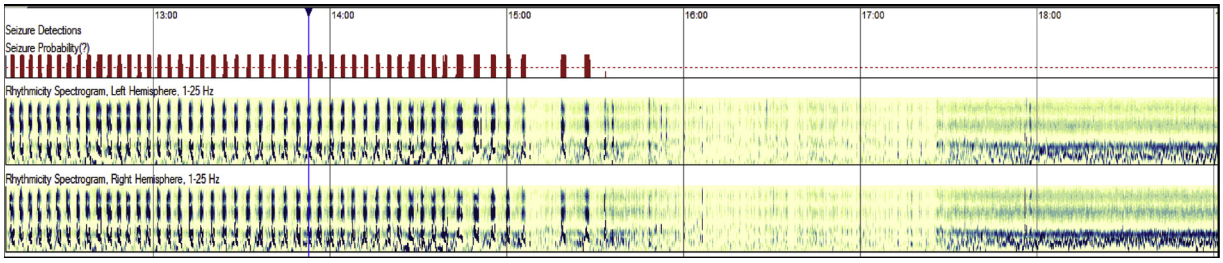


**Fig. 1. EEG Spectrogram.** Spectrogram demonstrating 19 seizures/hr followed by optimal seizure control as sedation is initiated (arrow). The patient's last seizure occurs around 15:30. There normalization of the EEG background two hours after seizure cessation.

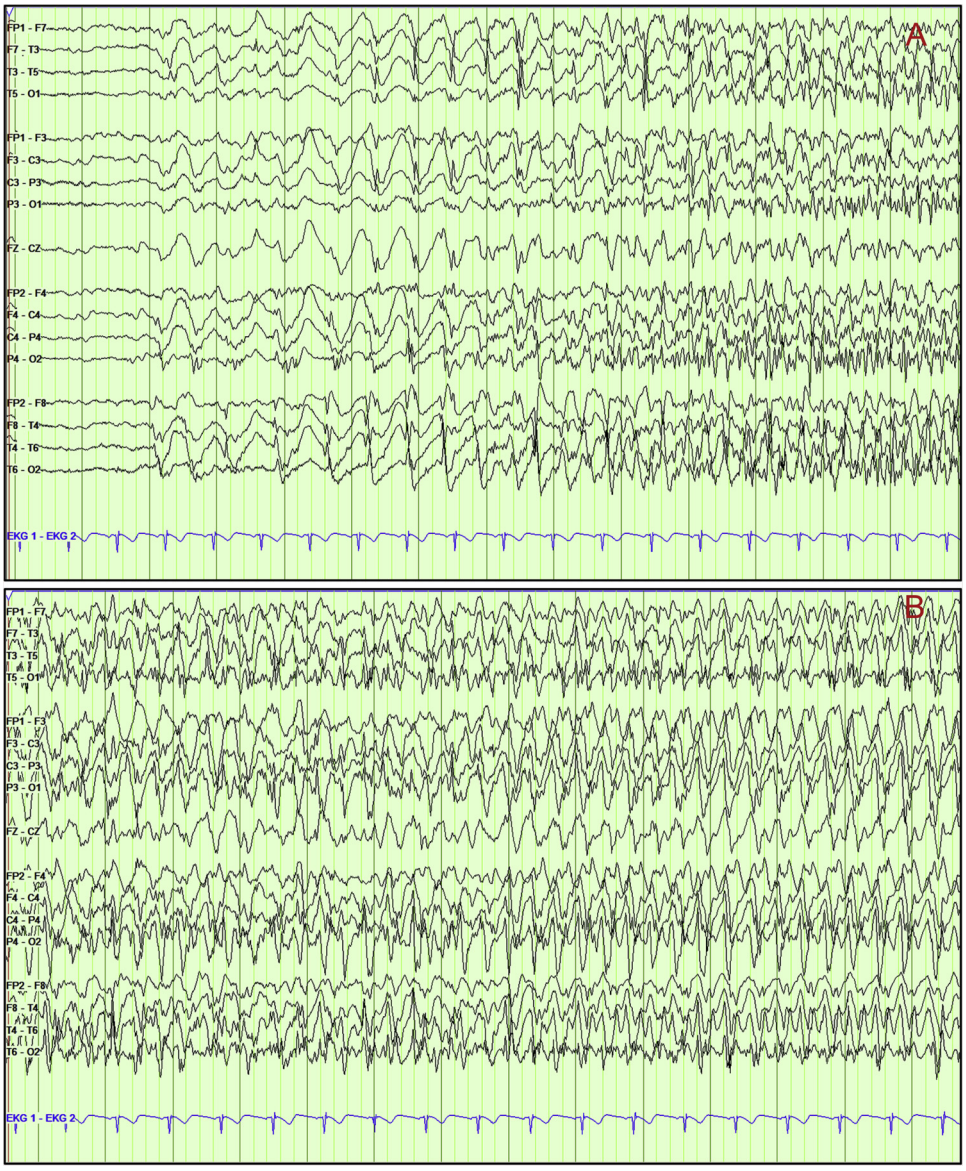


**Fig. 2. Extended EEG Monitoring. A)** Right posterior quadrant discharges with intermixed delta that spread to involve the bilateral hemispheres and transition into rhythmic higher voltage sharp theta/alpha activity (onset of seizure). **B)** This activity builds in amplitude and transitions to 2 Hz generalized spike and wave discharges, which occur approximately 20 times/hr. **C)** Burst suppression with propofol (at a rate of 50 mcg/kg/min) is achieved and is characterized by bursts of theta/delta activity with intermixed sharp contours and 10 s suppressions. **D)** As the sedation is weaned, there is a transition to bilaterally asymmetric runs of lateralized periodic discharges (LPDs) over the right > left posterior quadrants with superimposed fast and rhythmic activity (+FR). **E)** 24 h after the sedation is off, there is an emergence of a nearly continuous theta/delta background with frequent runs of rhythmic theta/delta with sharp components over the R posterior quadrant (LRDA + S).

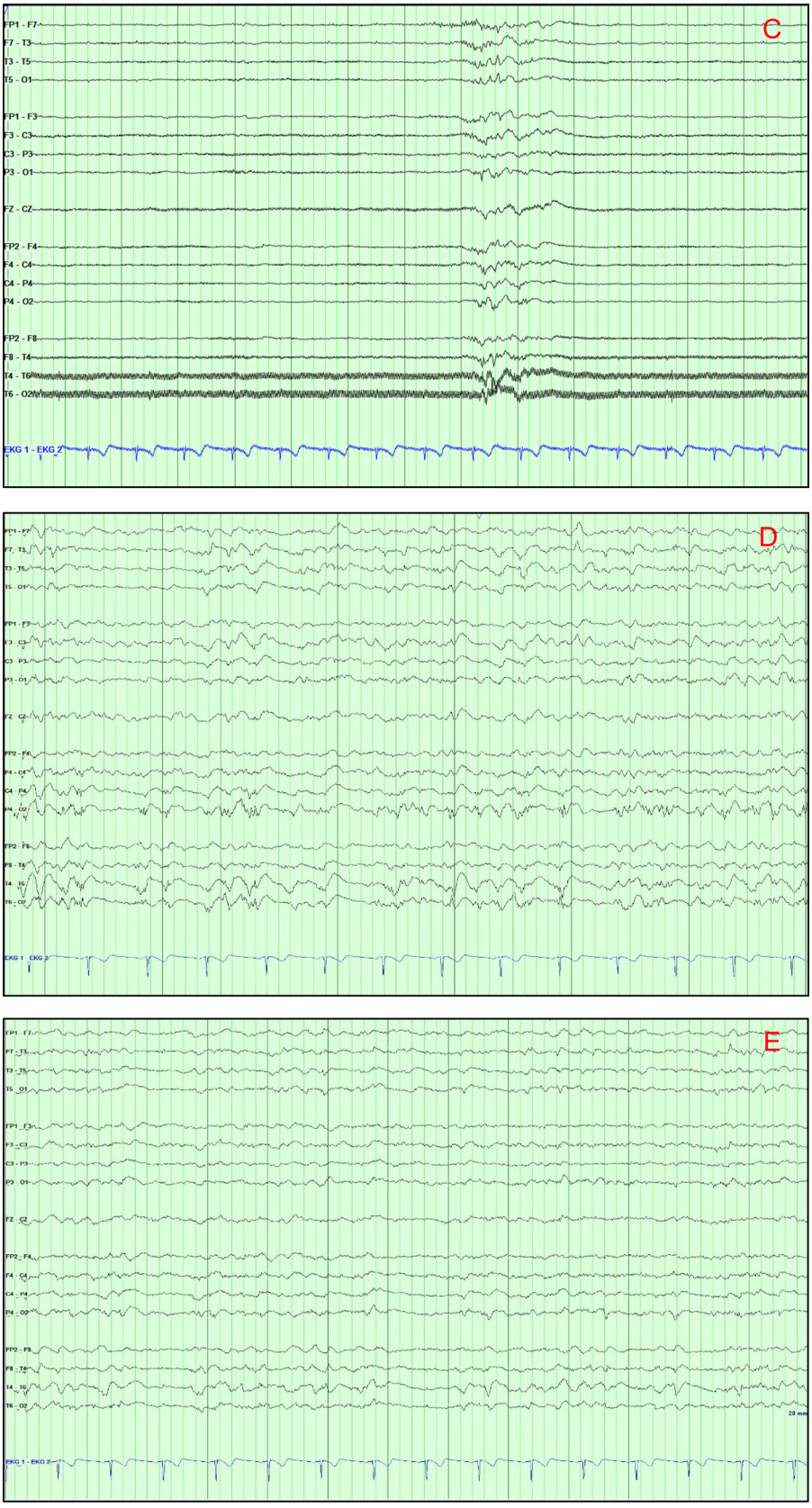


**Fig. 2.** (*continued*)

(Fig. 2C). Propofol was continued for approximately ninety minutes at which time weaning of anesthetic agents was initiated. Following weaning, the EEG pattern evolved into asymmetric runs of lateralized periodic discharges with superimposed fast and rhythmic activity (LPDs + FR) over the right posterior quadrant (Fig. 2D). After sedation was lifted, her mental status remained poor initially, but over the next few days, she continued to remain seizure-free (Fig. 2E).

The patient was extubated and she returned to her neurological baseline by the time of discharge. Overall, the etiology of her initial breakthrough seizures was felt to be related to lower seizure threshold due to hyperglycemia in the setting of uncontrolled diabetes (HbA1c was 11.1).

RSE remains a challenging condition to effectively manage given that adequate seizure control must be balanced against the known systemic toxicities of multiple AEDs. While the management of RSE is not well-defined, an aggressive early approach employing the use of third and fourth line agents is often preferred. Among these agents are intravenous general anesthetics including midazolam, propofol, and barbiturates. Although no intravenous agent is clearly superior, the goal of these agents is to induce a therapeutic coma, allowing for burst suppression. Burst suppression has met with mixed results, often with little benefit and prolonged hospital stay [3]. Moreover, the duration that burst suppression should be maintained is not established. Prolonged burst suppression increases the need for advanced ventilatory and cardiovascular monitoring and increases the likelihood for systemic toxicities to manifest [2]. While many practitioners apply burst suppression for 24–48 h, this is not well supported by the literature [1]. The scenario presented here highlights ultra-short burst suppression as an effective means to control RSE. In this case, seizure control was obtained within two hours of initiating burst suppression. Short periods of burst suppression may act as a “reset switch” for SE through rapid modulation of γ-aminobutyric acid receptors, thereby breaking the refractory nature of SE once it ensues. Compared with protracted burst suppression strategies, ultra-short burst suppression mitigates the adverse effects of general anesthetics such as propofol infusion syndrome [2]. Herein, we favor a more aggressive approach to anesthetic weaning compared with traditional methods of prolonged coma, especially when the underlying cause of RSE is reversed. Our patient also had known epilepsy, which has been shown in one study to have favorable outcomes in SE compared to patients with no prior epilepsy [4]. In some cases, truncated burst suppression can be trialed prior to attempting standard burst suppression duration (24–48 h). Although the patient’s age and other comorbidities prompted the decision to attempt ultra-short burst suppression, future studies aimed at determining which patients are appropriate candidates of this therapy are warranted.

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## Informed consent statement

Informed consent was obtained for participation in this study and subsequent publication of this manuscript.

## Conflict of interest declaration

None.

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