

# Ketamine suppresses spreading depolarizations in a case of severe brain trauma

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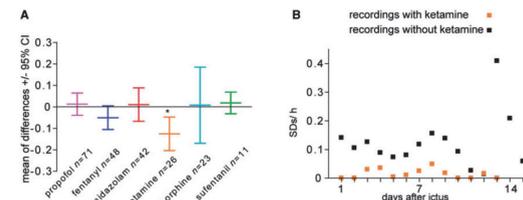
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## Introduction

- Spreading depolarizations (SDs) have been intensively studied as a causative mechanism of lesion development and excitotoxicity in animal models, and translational studies have demonstrated even greater relevance to human brain injury.
- A hurdle to broader clinical application of SD monitoring – and patient benefit – has been identification of effective treatments.
- Retrospective clinical studies have provided evidence that the S-enantiomer formulation of ketamine has a strong effect to block SDs, but effects of the racemic formulation available in the U.S. are unknown.



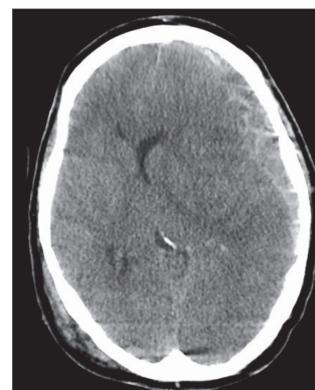
**Figure: Retrospective study of effect of analgo-sedatives on spreading depolarizations after acute brain injury.** 115 patients with brain trauma, aneurysmal subarachnoid hemorrhage, or malignant hemispheric stroke underwent ECoG monitoring of SDs in a multi-center study. SD incidence was retrospectively analyzed with respect to analgo-sedative drugs used in patient care. **A:** Periods of ketamine administration were significantly associated with decreased odds of SD occurrence [OR: 0.38 (0.18-0.79), p=0.01]. Effects of midazolam, propofol, sufentanil, and morphine were not significant (OR's 0.89-1.28). **B:** Ketamine effects were consistent over time post-injury. From: Hertle et al., *Brain* 135:2390-2398, 2012.

## Conclusions

This case provides striking evidence for the potency of racemic ketamine to suppress SDs, even in the setting of severe injury with refractory elevated ICP. There has been resistance to ketamine use for sedation in brain-injured patients due to historical fears that it may cause ICP elevation. However, these views have been refuted in randomized studies, and no adverse effects were observed in this case.

## Case Presentation

- A 49-year-old male fell 30 feet and was withdrawing his upper extremities upon arrival to UCMC.
- Emergency surgery was performed for evacuation of a large left subdural hematoma and hemicraniectomy.
- Consent was obtained for participation in TRACK-TBI and SD-II research studies.
- A subdural electrode strip was placed on the left inferior frontal gyrus to monitor SD, ICP/PtiO<sub>2</sub> probes were placed through a bolt in the right hemisphere, and scalp EEG was obtained.



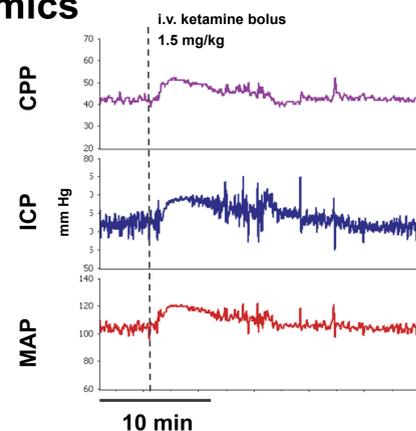
Admission CT



Intraoperative Photo

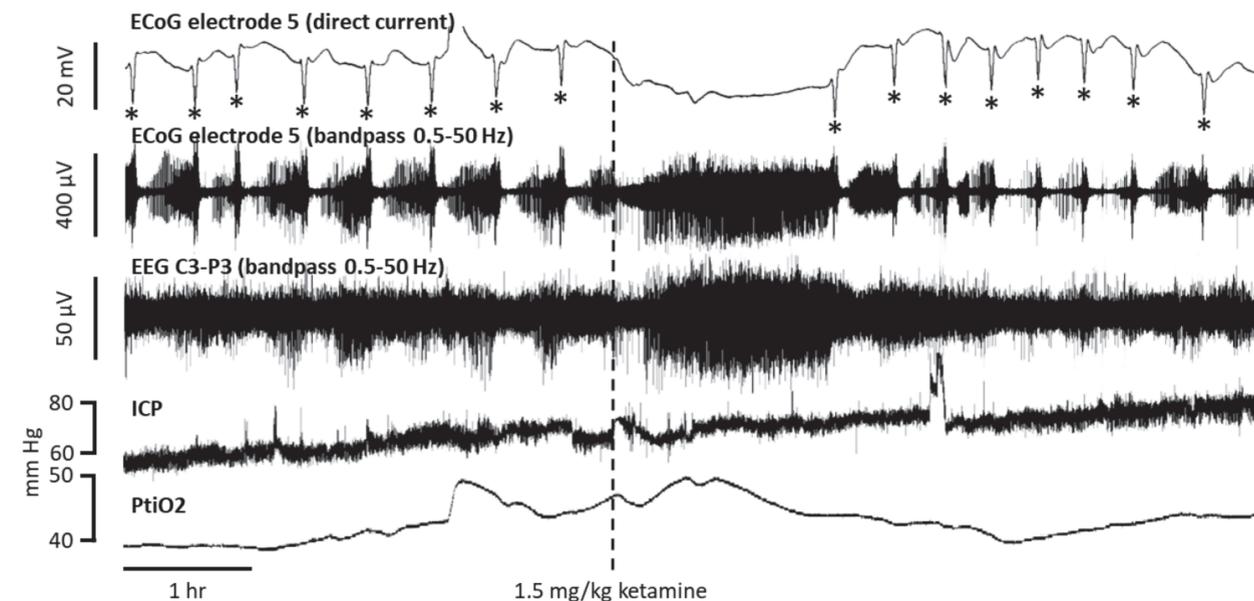
## Effect on Hemodynamics

**Figure:** Ketamine bolus transiently improved cerebral hemodynamics by raising mean arterial pressure (15 mm Hg) and cerebral perfusion pressure (10 mm Hg). Values returned to baseline levels within 15 minutes.



## Effect on Spreading Depolarizations

- From the start of ECoG after emergency neurosurgery, SDs (n=55) recurred continuously in the injured hemisphere at regular intervals of 20 (±6) min for 18 hr.
- To maximize sedation while preserving arterial pressure, a 1.5 mg/kg intravenous bolus of racemic ketamine was given.
- **After the ketamine bolus was given, the next expected SD did not occur, SDs remained suppressed for 2 hr, and both EEG and ECoG amplitudes recovered.**
- Subsequently, SDs resumed at regular intervals of 23 (±6) min, totaling 50 SDs in the following 19 hr. EEG returned to a state of depressed amplitude.
- Ketamine was not continued due to a family decision to withdraw care.



**Figure:** Electroencephalography (ECoG Channel 5) shows recurrent SDs at regular intervals (\*) that are interrupted for 2 hr following ketamine bolus. Bandpass at 0.5-50 Hz shows associated spreading depressions. Note that EEG (C3-P3) amplitude fluctuations also reflect the recurrence and suppression of SDs. Intracranial pressure increased progressively from 55 to 75 mmHg over the period shown, and mean arterial pressure was maintained at 100-110 mmHg.

## Future Direction

The cumulative evidence suggests that a prospective, multi-center trial of ketamine for suppression of spreading depolarizations is now warranted.

