Ketamine Inhibits Cortical Spreading Depolarization in Acute Brain Injury: A Prospective Randomized Multiple Crossover Trial.

Andrew Phillip Carlson MD MS-CR; Mohammad Abbas MD; Rob Alunday MD; Fares Qeadan PhD; C. William Shuttleworth MD

Department of Neurosurgery, University of New Mexico School of Medicine

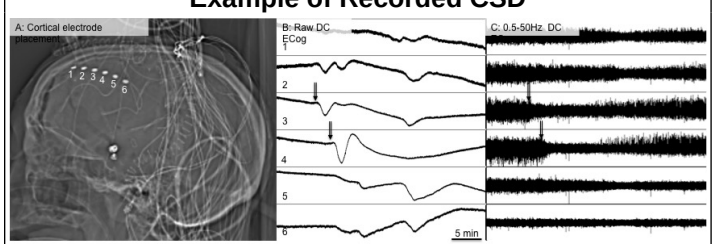
Introduction

Retrospective clinical data support a therapeutic effect of ketamine in suppression of CSD[1]. Animal and slice data strongly support this targeted efficacy on CSD. We present the results of the first prospective clinical trial testing the role of ketamine used for clinical sedation on occurrence of CSD after brain injury.

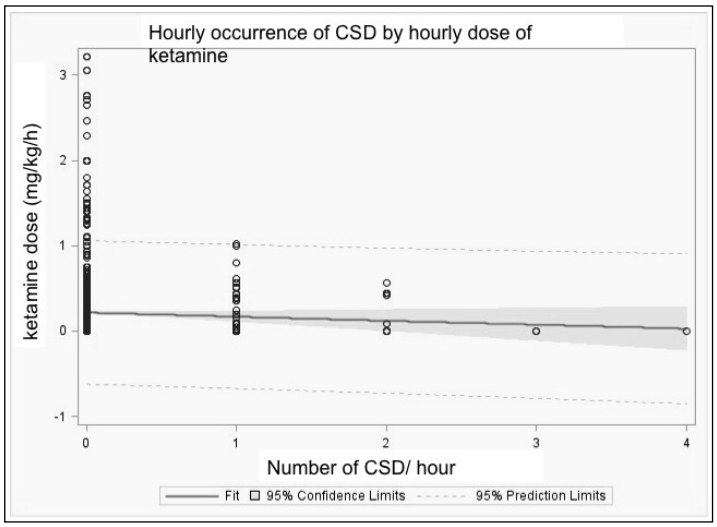
Methods

10 subjects with aneurysmal subarachnoid hemorrhage (SAH) or severe traumatic brain injury (TBI) or were recruited. A 1x6 ECog strip was placed at the time of craniotomy and subjects were then placed on a randomized alternating 6 hour schedule of ketamine or other sedation agent. Ketamine dose was adjusted to clinical effect and left at a subanesthetic basal dose if no sedation was required (0.1mg/kg/h.) CSD was scored using standard criteria, blinded to ketamine dosing. Occurrence of CSD was then compared to the hourly dose of ketamine to determine the effect of ketamine on CSD occurrence.

Example of Recorded CSD



The lateral scout film (A) shows the position of the electrode strip. The raw DC signal traces (B) show the propagating DC shift (arrows). Filtered data (C) show the characteristic depression of high frequency ECog signal



Results

Successful ECog recordings were obtained in all 10 subjects—8 with SAH and 2 with TBI. There was a total of 1642 hours of observations with adequate ECog— 833 off ketamine and 809 on ketamine. Hours on doses of less than 1.15mg/kg/h were associated with a highly significant increased risk of CSD compared with hours on doses of 1.15mg/kg/h or more (OR=13.838, 95% CI= 1.99-1000). A decrease of 0.15 mg/kg/h in dose was found to be associated with two-fold increase in the odds of CSDs (OR=1.973, 95% CI= 1.265-3.503). There was no significant effect of ketamine on the mean duration of depression after CSD (F=2.62, p=0.11).

Conclusions

Ketamine effectively inhibits CSD after acute neurologic injury (SAH and TBI) in a dose dependent fashion. These data also demonstrate the feasibility of using CSD as a surrogate measure in future studies prior to large-scale studies of CSD directed therapy on outcome.

Learning Objectives

1)Understand that cortical spreading depolarization occurs after acute neurologic injury and had been proposed to result in worse outcomes

2)Describe the dose dependent effect of ketamine on suppression of CSD

References

1 Hertle ED, Dreier JP, Woitzik J, et al. Effect of analgesics and sedatives on the occurrence of spreading depolarizations accompanying acute brain injury. Brain. Aug 2012;135(Pt8):2390-2398.