



Treatment of Super-Refractory Status Epilepticus: The Sooner the Better with Less Adverse Effects

Efficacy and Safety of Ketamine in Refractory Status Epilepticus.

Rosati A, L'Erario M, Ilvento L, Cecchi C, Pisano T, Mirabile L, Guerrini R. *Neurology* 2012;79:2355–2358.

OBJECTIVE: To evaluate the efficacy and safety of ketamine (KE) in the management of refractory convulsive status epilepticus (RSE) in children. **METHODS:** In November 2009, we started using KE for treating all children consecutively referred for RSE. Clinical and treatment data were analyzed. **RESULTS:** Between November 2009 and June 2011, 9 children with RSE received IV KE. In 8 patients, SE had persisted for more than 24 hours (super-refractory RSE), with a median of 6 days (mean 8.5 ± 7.5 ; range 2–26 days). Prior to KE administration, conventional anesthetics were used, including midazolam, thiopental, and propofol in 9, 5, and 4 patients each. Median dose of KE in continuous IV infusion was 40 $\mu\text{g}/\text{kg}/\text{min}$ (mean 36.5 ± 18.6 $\mu\text{g}/\text{kg}/\text{min}$; range 10–60 $\mu\text{g}/\text{kg}/\text{min}$). Midazolam was administered add-on to prevent emergence reactions. The use of KE was associated with resolution of RSE in 6 children. None of the patients experienced serious adverse events. Among the 3 individuals who did not respond to KE, 2 were cured by surgical removal of epileptogenic focal cortical dysplasia. **CONCLUSION:** In this small, open-label, unblinded series with no concurrent control group, KE appears effective and safe in treating RSE in children. Larger, randomized studies are needed to confirm data emerging from this preliminary observation. **CLASSIFICATION OF EVIDENCE:** This study provides Class IV evidence that IV KE can be effective in treating children with RSE (no statistical analysis was done).

Commentary

One of the areas within the field of epilepsy upon which there is universal agreement is the importance of avoiding the adverse effects of continuous, uncontrolled seizures due to the demonstrated or feared consequences on the brain, including exacerbation of chronic seizures, and new or chronic neurological disabilities (e.g. cognitive, motor), and systemic that can lead directly to mortality. Thus, there is no disagreement regarding the necessity of terminating convulsive and nonconvulsive seizures as soon as possible. That is where the consensus ends. The definition of 'status epilepticus' (SE) remains based in custom without consideration of evidence-based consequences and continues to range from 5 to 30 minutes in the modern literature. Similarly, the designation 'refractory status epilepticus' (RSE) was created to describe continuous seizures (independent of type, repetitive, etiology) not responsive to arbitrarily defined first- and second-line medications. Most recently, 'super-refractory SE' (SRSE) has been used to describe status epilepticus that continues beyond 24 hours following initiation of an anesthetic agent (1). The definition is purely operational and is too new to have an acquired evidence-based or even international consensus.

Why do—and should—we have or care about these descriptors? Ultimately, the answer lies in utility in the design, implementation and evaluation of treatment pathways to optimize outcomes.

The state of the literature regarding the treatment (2) and outcome (3) of RSE/SRSE has been recently summarized in comprehensive reviews in which it is noted that SRSE occurs in approximately 15% of adults. The frequency in children is unknown but certainly occurs in some fraction of those that are refractory to first- and second-line therapies. In that recent review, it was documented that the vast majority of reported cases of SRSE (920/1171, 79%) were treated with pentobarbital, midazolam, or propofol. Ketamine accounted for 17 cases in 7 published reports with resolution of seizures in 82%. Its potential neuroprotective effects support the use of this anesthetic agent as an NMDA receptor antagonist, in addition to its anticonvulsant properties. A significant contribution to our knowledge regarding the utility of ketamine in children has been provided by the recent report of Rosati and colleagues. This is the largest and best characterized series of children in whom ketamine has been used for refractory or SRSE. The study population is a familiar (and all too common) subset of children with epilepsy intractable to medications; that is, those with epileptic encephalopathies and motor dysfunction that are of unknown and known (e.g. structural brain abnormalities, mitochondrial cytopathy) etiologies. Ketamine was effective in achieving clinical and electrographic resolution of seizures in 6 of 9 children after days to weeks of convulsive seizures



not controlled with more conventional agents as per a RSE protocol. Adverse effects were limited to increased salivation and liver enzymes. As there was no randomization or control methodology, it is not possible to assess how ketamine fared compared to other potential therapies.

The effectiveness of ketamine for seizure control (similar to all other anesthetic agents) in SE, RSE, and SRSE in relatively small series of children and adults has been well described in this manuscript and the above-noted reviews. Is this surprising, and how does this information inform our treatment of children and adults with uncontrolled, continuous convulsive seizures? The answer to the first query is straightforward and succinctly stated by Shorvon and Ferlisi: “All anaesthetic drugs, if used in high enough doses, will result in a depth of anaesthesia sufficient to abolish seizure activity” (3). This is followed by the recognition that failure usually occurs “because the appropriate dose cannot be reached because of side-effects (notably hypotension or cardio-respiratory depression)” (3). This reality is strikingly similar to the manner in which we select and adjust maintenance of anti-epileptic drugs not on evidence-based differences in efficacy but rather according to the known adverse effects profiles, put in the clinical context of the individual patient. Although existing treatment protocols for RSE/SRSE most commonly use midazolam, pentobarbital, or propofol for days to weeks prior to the consideration of other agents, should ketamine be considered for earlier use, based upon

its known anti-seizure effects, theoretical neuroprotective properties, and low adverse-effect profile—a thought that has recently been made by others (2, 4)? The most common dose-limiting adverse effects of midazolam, propofol, and pentobarbital include hypotension, and cardiac and respiratory depression, which are not commonly a problem with ketamine. One could suggest that midazolam followed by ketamine in the first 24 hours of RSE would be a reasonable sequence in a protocol for RSE. This should be done in a manner that allows assessment of the overall efficacy of this approach, either by using historical controls or, better yet, in a randomized and controlled fashion.

by Jeffrey Buchhalter, MD, PhD, FAAN

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