Early Administration of Ketamine in Refractory Status Epilepticus

Kayla Moody

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Abstract

Purpose: While protocols regarding how to treat status epilepticus (SE) has been universally accepted, management of refractory status epilepticus (RSE) is far from being evidence-based. Ketamine (KET), a NMDA-antagonist, may have a role in RSE when other conventional anesthetics fail due to its unique pharmacodynamic properties and good safety profile.

Methods: Exhaustive search of available medical literature was performed using MEDLINE-Ovid, MEDLINE-PubMed, Psych INFO, Web of Science, and CINAHL for relevant articles from 2012-2017 using keywords “ketamine” and “status epilepticus.” Additional criteria for consideration: articles applicable to the topic and published in the English language. Exclusion criteria includes all opinion articles, preclinical data, protocol articles, and case studies. Studies were then assessed for quality using GRADE criteria.

Results: The 4 studies reviewed found a good response rate ranging from 64-80% when KET was used as the first- or second-line agent in RSE. Furthermore, all studies found a good safety profile of KET at high doses and long duration of infusion. Although initial response rate of RSE to early administration of KET is high, all 4 studies have severe limitations.

Conclusion: Currently, RSE algorithms are inadequate and leave providers to choose the best course of action. Earlier introduction of KET after failure of first- and second-line agents shows promise to control RSE and avoid intubation and ventilation. This area of study needs larger, prospective, and randomized trials that clearly designate and follow a protocol to assess adequate efficacy of early administration of KET in RSE.

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Degree Name
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Keywords
ketamine, status epilepticus, children, adults, refractory status epilepticus

Subject Categories
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Early Administration of Ketamine in Refractory Status Epilepticus

Kayla Moody

A Clinical Graduate Project Submitted to the Faculty of the
School of Physician Assistant Studies
Pacific University
Hillsboro, OR
For the Masters of Science Degree, August 2018
Faculty Advisor: Saje Davis-Risen, PA-C
Clinical Graduate Project Coordinator: Annjanette Sommers, PA-C, MS
Biography

[redacted]
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Acknowledgements

[redacted]
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Table 1: Quality Assessment of Reviewed Studies

List of Abbreviations

AED antiepileptic drug
BS burst suppression
cEEG continuous EEG
EEG electroencephalogram
ETT endotracheal tube intubation
GCSE Generalized Convulsive Status Epilepticus
ICP intracranial pressure
IV Intravenous
IVAD IV anesthetic drug
KET Ketamine
MDZ Midazolam
PRIS Propofol infusion syndrome
PRO Propofol
PTB Pentobarbital
RSE Refractory Status Epilepticus
SE Status Epilepticus
SRSE Super Refractory Status Epilepticus
Early Administration of Ketamine in Refractory Status Epilepticus

BACKGROUND

Status Epilepticus and Refractory Status Epilepticus Defined

Status epilepticus (SE) is a relatively common life-threatening emergency that can be defined as 5 or more minutes of continuous seizure activity or intermittent seizures without full recovery between episodes. The timing is disputed in older studies with references to SE seizures lasting at least 30 minutes. SE that is resistant to 2 antiepileptic drugs (AED) is defined as refractory status epilepticus (RSE), occurring between 30-43% of all patients that initially present with a SE episode. RSE is associated with prolonged hospital length of stay, increased costs, and significant morbidity and mortality.

Current Treatment Protocol

To provide guidance regarding treatment of SE, the Neurocritical Care Society and American Epilepsy Society have developed evidence and consensus-based guidelines to assist with therapy. These guidelines focus on the use of AEDs – IV benzodiazepines, phenytoin, fosphenytoin, and phenobarbital – at weight-based loading doses (see Figure 1 and 2). AEDs modify the excitability of the nervous system by inhibiting sodium currents or by enhancing GABA (gamma-aminobutyric acid) effects through the GABA$_A$ receptor.
Once these measures fail to control a seizure, RSE treatment is based on type of seizure (convulsive vs. nonconvulsive) and the individual patient’s comorbidities.\textsuperscript{10} There is a consensus that all patients with RSE require respiratory and hemodynamic monitoring and support in addition to continuous EEG (cEEG) monitoring,\textsuperscript{1} but data\textsuperscript{10,11} supporting specific therapy is limited and even varies between medical centers based on provider preference. UpToDate\textsuperscript{12} lists the primary drugs for RSE as high-dose midazolam (MDZ), propofol (PRO), and barbiturates (eg, pentobarbital, thiopental, or phenobarbital). Factors that one must consider when selecting RSE therapy are comorbidities of the patient,\textsuperscript{13,14} type of seizure activity,\textsuperscript{10} pharmacokinetics of each drug,\textsuperscript{15} and drugs that have already been tried.

Additionally, treatment usually involves a combination of both AEDs and intravenous anesthetic drugs (IVAD), which may worsen prognosis due to compounding of side effects.\textsuperscript{15} Continuous intravenous (IV) infusion of conventional anesthetics is associated with respiratory depression that requires endotracheal tube intubation and cardiac depression causing hypotension and low cardiac output.\textsuperscript{16} This is based largely on the pharmacokinetics of conventional anesthetics, which rely on neuronal inhibition mediated largely through the GABA\textsubscript{A} receptor.

\textbf{cEEG Monitoring}

As stated above, cEEG monitoring during infusion is imperative to assess efficacy and guide titration of the drug, while overall directing the plan of care for the patient.\textsuperscript{17}
When asked about titration goals while using continuous infusion of AEDs, 56% of neurologists in the United States aim for the burst suppression (BS) pattern on the EEG, while 42% look for elimination of seizures without BS pattern. This suggests that resolution of SE is not always associated with a BS pattern; in fact, KET may cause its own morphological EEG changes that may potentially be used as a biomarker for RSE response in the future.

Pathophysiology and Neurobiology of RSE

Common causes of RSE are different than the former SE. While most SE cases are due to low AED levels, cerebrovascular disease, alcohol abuse, and CNS infections, the etiology of RSE is associated with conditions with a poorer prognosis, such as metabolic abnormalities, encephalitis, and CNS or systemic infections. Additionally, the pharmacokinetics associated with RSE are slightly different. Therefore, it would be appropriate to assume that different treatment would be necessary to manage RSE than SE. While most seizures can be terminated in a matter of minutes with inhibition of the GABA receptor, prolonged seizures cause inhibitory GABA receptors to internalize, while excitatory N-methyl-D-aspartate (NMDA) receptors, a type of glutamate receptor, are mobilized to the surface of the cell. This exchange in receptor dominance is thought to be the reason why conventional AEDs become less active and require higher doses over the long term. Higher doses of conventional anesthetics enhance adverse events such as hypotension, immunosuppression, and reduced gastrointestinal motility that require special monitoring, endotracheal intubation (ETT), and careful observation. In RSE cases treated with PRO, clinicians must monitor closely for signs of propofol
infusion syndrome (PRIS) – ie. metabolic acidosis, rhabdomyolysis, hyperlipidemia, or fatty liver.26

**Pharmacology of Ketamine**

Ketamine (KET) may play a role in RSE due to its pharmacodynamic properties. Its action is thought to be mediated through non-competitive blockade of the NMDA-receptor, but its full mechanism is still not fully understood.27 KET has equal amounts of 2 enantiomers (S)- and (R)-KET that have different pharmacodynamic properties. For example, (S)-KET has faster clearance that results in shorter duration of action and faster recovery, but has been shown to be no more effective than racemic KET.28 The racemic mixture seems to be more readily used and is available in 3 different concentrations: 10 mg/ml, 50 mg/ml, and 100 mg/ml and may be administered a variety of different routes.12

While KET has been avoided in certain clinical situations due to its stigma of use in veterinary medicine, abuse potential,29 and association with adverse events like hallucinations30 and increased intracranial pressure (ICP),31 it is an inexpensive drug32 that has proven that its unique properties allow it to be useful in a variety of different clinical applications.29,33 Furthermore, concern of ketamine use increasing ICP stems from limited, small sample sized studies34 that have since been challenged by a variety of published studies.35,23 Additionally, hallucinations, which occurs in about 20% of the adult population36 and even less frequently in the pediatric population, may be reduced with premedication with benzodiazepines or other AEDs.32,37
The literature has provided good evidence that KET is both safe and efficacious in both adult and pediatric populations. For example, thanks to its sympathomimetic effects, KET has less hemodynamic complications, is considered neuroprotective in concomitant traumatic brain injuries, improves cerebral perfusion, has minimal effects on central respiratory drive and produces airway relaxation, has anti-inflammatory properties, and may avoid the need for ETT. Animal models have demonstrated later efficacy (1 hour) compared to early efficacy (15 min) of ketamine, implying that the receptor changes that occur in RSE must occur for KET to be effective.

**Rationale for Conducting this Systemic Review**

A variety of studies show that ketamine plays a role in RSE, especially as it is the only NMDA antagonist currently used in RSE therapy. An increasing number of clinicians are not only advocating ketamine use, but earlier introduction of ketamine in RSE therapy. As Zeiler (2015) states, “one could extrapolate that with the reasonable success obtained in the cases summarized […] and with earlier implementation of NMDA receptor antagonism, less glutamate mediate[d] excitotoxicity would occur, and potentially SE would be less refractory.” Unfortunately, it seems the majority of the medical community is still reluctant to even use ketamine in the first place, regardless of the proven benefits of KET administration over conventional anesthetics such as vasopressor sparing anesthetic effects, analgesic effects, and lack of significant documented adverse events. Based on these thoughts, this systematic review looks at articles that focus on early administration of KET during RSE treatment.
METHODS

An exhaustive literature search was performed using MEDLINE-Ovid, MEDLINE-PubMed, Psych INFO, Web of Science, and CINAHL for relevant articles from 2012-2017. Keywords included: “ketamine” and “status epilepticus.” Additional inclusion criteria for consideration: articles applicable to the topic and those published in the English language. Exclusion criteria included all opinion articles, preclinical data, protocol articles, and case studies. In addition to database searches, references from select articles were reviewed for potential relevant sources. The selected articles were assessed using GRADE criteria to address quality of evidence.42

RESULTS

The database search produced 204 articles. After eliminating all duplicate articles among the databases, a total of 4 articles16,22,23,30 were found to be relevant to the clinical question and met all eligibility criteria. See Table 1.

Rosati et al (2012)

This unblinded series30 with no concurrent control group (Class IV Study) looked at 9 children (age range: 10 months – 10 years old) with RSE that received IV KET. The majority of these children were chronic epilepsy patients. From November 2009 to June 2011, Rosati et al endorsed a treatment protocol for RSE that included IV KET infusion. This protocol was as follows: two IV KET boluses were administered 5 minutes apart followed by a continuous infusion. Based on clinical and EEG response, the infusion
dose was increased every 10 minutes up until a predetermined maximum dose. Midazolam was added on to prevent KET side effects and blood tests were performed regularly.  

All cases were pre-treated with at least 1 conventional anesthetic. KET was given within a median time of 6 days (range: 5 hours – 26 days) of SE therapy and the median duration of KET infusion was 6 days (range: 3-17 days). KET was responsible for resolution in 6/9 (67%) children, and none of these 6 responders had a SE relapse. Of note, BS pattern was obtained in 5/6 (83%) of KET responders. Additionally, none of the 9 children treated experienced severe adverse events but a slight increase of saliva production occurred in all patients during KET administration.  

**Synowiec et al (2013)**  
This analysis was performed retrospectively by reviewing adult patient charts that 1) indicated RSE based on billing codes assigned at discharge and 2) were between Jan 2003 and December 2011. These charts were further reviewed to indicate which patients with RSE were treated with KET. After exclusion of patients with inadequate data, total number of patients with outcome data was 11. The majority of these patients had chronic epilepsy.  

Prior to use of KET, each patient was being treated with a continuous infusion of IVAD and were placed on a cEEG monitor (10/11 patients) or intermittent EEG monitor. Most patients were bolused with KET (10/11) prior to initiation of continuous KET
infusion. Continuous infusion dosing and maximum dose given varied based upon preference on clinician and clinical response.22

KET was the second IVAD used in 8/11 (73%) cases. Attempts were made in all cases to wean prior IVAD once KET had been introduced, succeeding in 8/11 (73%) cases. Overall, KET was the last AED used prior and caused resolution of RSE in 7/11 (64%) cases. Additionally, 7/11 cases developed hypotension prior to KET that required treatment with vasopressors; once KET was added to RSE therapy, 6/7 (85%) patients could be weaned from the pressors.22

**Gaspard et al (2013)**

This study23 looked at RSE cases treated with IV KET between 1999 and 2012 in a multicenter retrospective review of medical and EEG records. Information was obtained from a total of 60 RSE episodes (from 46 adults and 12 children) using a standardized datasheet from 10 medical centers in both North America and Europe. This study focuses on patients with NORSE (new-onset refractory status epilepticus) and acute brain injury, an etiology that carries a worse prognostic outcome than cases occurring in the setting of chronic epilepsy.23

This study’s protocol always used KET as a part of a multi-drug regimen, and its introduction into RSE therapy usually occurred after a mean of 9 days of SE. There was a wide variability of how it was administered (with and without use of loading doses, duration of infusion, infusion amount).23
KET was likely or possibly responsible for resolution of RSE in 19/60 (32%), with 7/60 (12%) cases being likely due to KET. Additionally, resolution rate was higher when KET was used as third or fourth-line agent in SE (first or second-line in RSE), and was responsible for cessation of RSE in 6/10 (60%) of cases. Overall, Gaspard et al noticed that a likely response was not observed when 1) infusion rates of KET were lower than 0.9 mg/kg/h, 2) KET was introduced 8+ days after SE onset, or 3) after failure of 7+ drugs.\textsuperscript{23}

Of the cohort, 52/60 were treated with vasopressors prior to KET; 6/52 were weaned, while 21/52 increased vasopressor dosage after initiation of KET. Younger age and response to KET were associated with lower mortality. There was no difference in functional outcome in survivors based on if they responded to KET or not; therefore, duration and dosage of KET was not related to mortality. KET was discontinued in 4/60 cases due to suspected treatment-related reactions, such as supraventricular tachycardia, atrial fibrillation, and a similar infusion reaction to PRIS, but can be related to concurrent use of anesthetics.

\textbf{Ilvento et al (2015)}

This study\textsuperscript{16} is an extension of the Rosati \textit{et al} (2012)\textsuperscript{30} study. Between November 2009 and February 2015, they looked at 13 children (age range: 2 months – 11 years old) with RSE that were treated with IV KET. Most of these children were chronic epilepsy patients. Eight children were treated once, 2 were treated twice, and 3 were treated 3
times, for a grand total of 19 different treatments. 10/19 of these treatments were with (S)-KET, while the remaining 9/19 were treated with racemic KET.\textsuperscript{16}

The use of KET was associated with RSE suppression in 14/19 (74\%) episodes, and the EEG BS pattern was seen in 10/19 (53\%) episodes. There were 5 children that were treated with IV KET prior to all conventional anesthetics to help avoid mechanical ventilation. SE control was obtained in 4/5 (80\%) of these children, thus eliminating the need for intubation.\textsuperscript{16}

**DISCUSSION**

The mortality rate for RSE ranges from 16-39\% and etiology of SE is still the primary and most important determinant of outcome.\textsuperscript{6,43,44} Even so, it is not advised to stop treatment based on duration of SE, as most patients suffering from RSE for extended periods of time may recover with a functional outcome.\textsuperscript{6} During a 1-year follow-up, 50\% of RSE treated cases in the ICU returned to baseline, whereas 30\% of cases had functional defects and 20\% died.\textsuperscript{43} Long-term mechanical ventilation,\textsuperscript{45,17} older age, no prior history of seizures or epilepsy, specific seizure types, and coma-induction predicted a worse prognosis,\textsuperscript{45-47} but was not necessarily predictive of a worse outcome.\textsuperscript{43}

As of now, there is no established protocol for treatment of RSE. Studies\textsuperscript{43} have shown that the longer SE goes untreated, the worse the prognosis. Therefore, rapid initial treatment can be correlated to better response to treatment and lower mortality rates overall.\textsuperscript{48} It is imperative that we solidify a recognized RSE protocol, as patients tend to
fare worse when a recognized protocol was not followed. Unfortunately, there are no published randomized trials comparing various treatments, and the optimal treatment of RSE is far from being evidence based medicine.

Shelth and Gidal (1998) first described successful RSE treatment with IV KET in a 13-year-old girl with unknown etiology. Since that time, most studies published have been pre-clinical studies, case reports, or small sample studies. The above reviewed studies focus not only incorporating KET into RSE treatment, but advocating for earlier treatment with it. The 4 studies found response rates ranging from 64%-80% when KET was used as the first- or second-line medication in RSE. Yet these articles are no exception to the previous research limitations, as they themselves are small, non-blinded studies with subject heterogeneity. As non-established treatment is usually administered when RSE is most severe, clinicians cannot rule out spontaneous improvement of RSE. Additionally, concomitant use of many medications during RSE therapy makes it hard to assess efficacy of KET alone, and therefore one cannot rule out a cumulative or delayed effect of other drugs given.

Overall, there is a reluctance in the medical community to use KET, either due to its reputation of causing adverse effects in certain populations or due to lack of familiarity with the drug and its mechanism. In fact, in a recent survey of neurologists, neurosurgeons, and intensivists across Canada, 76% viewed KET as an experimental drug. Yet, in the same survey, 68% stated they would consider using KET (again) for SE, with 48% stating that they would even consider using it earlier during treatment.
Additionally, countless articles have found that KET at high doses and long duration is safe for use in both adults and children, even rivaling the potential safety of conventional anesthetics. It has proven to be respiratory, cardio-, and neuroprotective. Due to these unique capabilities, KET use may avoid the requirement for intubation and/or vasopressors, decreasing morbidity and mortality of those treated for RSE.

Although larger, prospective, and randomized trials that clearly designate and follow a protocol are needed to help further evidence-based management of RSE, there is a lack of randomized control trials that have been published. Rosetti et al (2011) initiated a randomized controlled trial (RCT) investigating the best agents for RSE, but it was aborted after 3 years due to funding issues and difficulties enrolling a large enough cohort. They realized that they needed participation from a larger number of resources in order to increase their enrollment. Therefore, they created a multicenter randomized sequential trial, Rosati et al (2016). Although it is still in the recruitment stage, this study is aimed at assessment of efficacy and safety of KET compared to conventional anesthetics (midazolam, propofol, barbiturates) in the treatment of RSE in children. Unfortunately, these are not the only RCTs that have struggled to recruit participants, as RSE is a rare condition. However, Zeiler and West show that 74% of respondents would participate in a prospective study evaluating early KET administration in RSE, showing that there is an excitement regarding the possibilities of KET in the advancement of RSE therapy.
CONCLUSION

SE is a neurological emergency that requires immediate treatment as means to reduce sequela. Guidance in the treatment of SE is well documented and focuses on the use of AEDs. Yet when these epileptic episodes become refractory to treatment with conventional anesthetics, providers are left using their best judgement for further management based on patient’s comorbidities, seizure type, and response to prior drugs.

While current guidelines for treatment of RSE are lacking, recent studies are allowing us better understanding of how to control RSE. The studies presented during this systematic review argue for earlier introduction of KET after failure of first- and second-line agents, which shows promise to control RSE and avoid intubation and ventilation. Nevertheless, its use needs to be investigated further with a standardized treatment algorithm in prospective, randomized control trials.

REFERENCES


Figure 1. Management of SE and RSE\textsuperscript{12}

Treatment of convulsive status epilepticus in adults

<table>
<thead>
<tr>
<th>Initial assessment</th>
<th>Initial therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Neurologic examination</td>
<td>• In first IV:</td>
</tr>
<tr>
<td>• General evaluation with attention to respiratory and circulatory status</td>
<td>• Lorazepam 0.1 mg/kg IV or 4 mg IV (max 2 mg/minute)</td>
</tr>
<tr>
<td>• O2 &amp; mechanical ventilation PRN</td>
<td>• Alternatives:</td>
</tr>
<tr>
<td>• IV catheters inserted (at least two)</td>
<td>• Diazepam 0.15 mg/kg IV up to 10 mg per dose (max 5 mg/minute)</td>
</tr>
<tr>
<td>• Blood work:</td>
<td>• Wait 1 minute for response then additional lorazepam PRN*</td>
</tr>
<tr>
<td>• Electrolytes, Ca, Mg, Phos, glucose, LFTs, CBC, toxicology, AED level(s)</td>
<td></td>
</tr>
<tr>
<td>• Fingerstick glucose</td>
<td></td>
</tr>
<tr>
<td>• Cardiac monitoring with pulse oximetry</td>
<td></td>
</tr>
<tr>
<td>• Frequent vital signs</td>
<td></td>
</tr>
<tr>
<td>• Consider glucose + thiamine IV</td>
<td></td>
</tr>
</tbody>
</table>

Correct metabolic abnormalities if present

<table>
<thead>
<tr>
<th>Second-line therapy</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>• Repeat fosphenytoin if given previously (5 mg/kg PE) or choose among first-line drugs not already given</td>
<td></td>
</tr>
<tr>
<td>• Intubation, mechanical ventilation</td>
<td></td>
</tr>
<tr>
<td>• Continuous blood pressure, cardiac monitoring</td>
<td></td>
</tr>
<tr>
<td>• Prepare for continuous midazolam or propofol infusion\textsuperscript{a}</td>
<td></td>
</tr>
</tbody>
</table>

Refractory status epilepticus\textsuperscript{b}

Begin continuous EEG monitoring

<table>
<thead>
<tr>
<th>Midazolam</th>
<th>Propofol</th>
<th>Pentobarbital</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Midazolam initial dose: 0.2 mg/kg IV bolus, given at 2 mg/minute</td>
<td>• Propofol infusion: 1 to 3 mg/kg loading dose, over 5 minutes</td>
<td>• Pentobarbital initial dose: 15 mg/kg IV over 10 minutes</td>
</tr>
<tr>
<td>• Continue infusion beginning at 0.1 mg/kg/hour; titrate upward to seizure freedom</td>
<td>• Continue infusion, titrated upward to seizure freedom</td>
<td>• Repeat as necessary until seizures stop</td>
</tr>
<tr>
<td>• May use infusion of up to 3 mg/kg/hour</td>
<td>• Rates may be as high as 10 to 12 mg/kg/hour but preferably for &lt;48 hours</td>
<td>• Then, pentobarbital 1 to 5 mg/kg/hour for 24 hours of secure freedom</td>
</tr>
<tr>
<td>• If seizures persist after 45 to 60 minutes, change to propofol or pentobarbital</td>
<td>• After seizure control, maintain for 24 hours</td>
<td>• Use vasopressor support if necessary</td>
</tr>
<tr>
<td>• Use vasopressor support if necessary</td>
<td>• If seizures persist after 45 to 60 minutes, change to pentobarbital</td>
<td>• Maintain therapeutic levels of phenytoin, phenobarbital, or both\textsuperscript{c}</td>
</tr>
<tr>
<td>• Maintain therapeutic levels of phenytoin, phenobarbital, or both\textsuperscript{c}</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*If no IV access:

• Midazolam 10 mg IM if weight >40 kg

In second IV:

• Fosphenytoin 20 mg/kg PE at 100 to 150 mg PE/minute\textsuperscript{b} OR
• Phenytoin 20 mg/kg at 25 to 50 mg/minute\textsuperscript{b} OR
• Valproic acid 30 mg/kg at 10 mg/kg/minute OR
• Levetiracetam 40 to 60 mg/kg (maximum 4500 mg) over 15 minutes

\textsuperscript{a}Preparation of continuous infusion in anesthetic setting.

\textsuperscript{b}Not first-line for refractory status.

\textsuperscript{c}Phenytoin and phenobarbital therapy is considered as a second-line therapy.
### Figure 2. Dosing of medications used in treatment of SE and RSE

<table>
<thead>
<tr>
<th>Treatment of nonconvulsive status epilepticus (NCSE) in adults</th>
<th>Initial dose</th>
<th>Re-loading dose</th>
<th>Maintenance dose</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Parenteral benzodiazepine choices (initial regimens)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lorazepam</td>
<td>0.1 mg/kg (up to 4 mg) IV bolus (up to 2 mg/min)</td>
<td>0.1 mg/kg (up to 4 mg)</td>
<td>N/A</td>
</tr>
<tr>
<td>Diazepam</td>
<td>0.15 mg/kg (up to 10 mg) IV bolus (up to 5 mg/min)</td>
<td>0.15 mg/kg (up to 10 mg)</td>
<td>N/A</td>
</tr>
<tr>
<td>Midazolam</td>
<td>0.2 mg/kg (up to 10 mg) intravenously</td>
<td>0.2 mg/kg (up to 10 mg) intravenously</td>
<td>N/A</td>
</tr>
<tr>
<td>Chlordiazepoxide&lt;sup&gt;4&lt;/sup&gt;</td>
<td>0.015 mg/kg (up to 1 mg) slow IV bolus (0.5 mg/min)</td>
<td>0.015 mg/kg (up to 1 mg)</td>
<td>N/A</td>
</tr>
<tr>
<td><strong>Non-sedating antiepileptic choices (initial regimens)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Phenytoin</td>
<td>20 mg/kg IV (up to 50 mg/min)</td>
<td>5 to 10 mg/kg up to a maximum cumulative dose of 30 mg/kg&lt;sup&gt;5&lt;/sup&gt;</td>
<td>5 to 7 mg/kg/d orally/IV, divided every 8 h</td>
</tr>
<tr>
<td>Fosphenytoin</td>
<td>20 mg PE/kg IV (up to 150 mg PE/min)</td>
<td>5 to 10 mg PE/kg up to a maximum cumulative dose of 30 mg/kg&lt;sup&gt;5&lt;/sup&gt;</td>
<td>5 to 7 mg PE/kg/d orally/IV divided every 8 h</td>
</tr>
<tr>
<td>Valproate</td>
<td>20 to 40 mg/kg IV (up to 5 mg/kg/min)</td>
<td>20 mg/kg</td>
<td>30 to 60 mg/kg/d orally/IV divided every 6 to 12 h&lt;sup&gt;6&lt;/sup&gt;</td>
</tr>
<tr>
<td>Levetiracetam</td>
<td>2500 mg IV (up to 5 mg/kg/min, typically given over 15 min)</td>
<td>1000 to 2000 mg</td>
<td>2 to 4 g/d orally/IV, divided every 6 to 12 h&lt;sup&gt;2&lt;/sup&gt;</td>
</tr>
<tr>
<td>Lamotrigine</td>
<td>200 to 400 mg IV (over 15 min)</td>
<td>200 mg</td>
<td>200 to 600 mg/d orally/IV, divided every 12 h 6&lt;sup&gt;7&lt;/sup&gt;</td>
</tr>
<tr>
<td><strong>Potential oral or nasogastric add-on non-anesthetic options</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Topiramate</td>
<td>100 mg orally every 12 h</td>
<td>300 to 800 mg/d orally, divided every 8-12 h</td>
<td></td>
</tr>
<tr>
<td>Gabapentin</td>
<td>300 mg orally every 8 h</td>
<td>1800 to 3600 mg/d orally, divided every 6-8 h</td>
<td></td>
</tr>
<tr>
<td>Prop each</td>
<td>75 mg orally every 12 h</td>
<td>150 to 600 mg/d orally, divided every 8-12 h</td>
<td></td>
</tr>
<tr>
<td>Clobazam</td>
<td>10 to 20 mg orally every 12 h</td>
<td>60 mg/d orally, divided every 12 h</td>
<td></td>
</tr>
<tr>
<td>Perampanel</td>
<td>6 to 12 mg orally every 24 h</td>
<td>Up to 12 mg orally every 24 h</td>
<td></td>
</tr>
<tr>
<td>Olanzapine</td>
<td>Up to 2400 mg/day orally, divided every 24 h</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Carbamazepine</td>
<td>300 to 600 mg orally every 12 h</td>
<td>1600 mg/d orally, divided every 12 h (tablets) or every 6 h (liquid)</td>
<td></td>
</tr>
<tr>
<td>Vigabatrin</td>
<td>Up to 3000 mg/day orally, divided every 12 h&lt;sup&gt;8&lt;/sup&gt;</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Continuous infusion anesthetic options in critically ill mechanically ventilated patients</strong></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Midazolam</td>
<td>0.2 mg/kg IV (up to 2 mg/min) every 5 min until seizures controlled or maximum dose of 2 mg/kg; followed by continuous infusion</td>
<td>N/A</td>
<td>0.05 to 2.9 mg/kg/h continuous IV infusion</td>
</tr>
<tr>
<td>Propofol</td>
<td>1 to 2 mg/kg IV every 5 min until seizures controlled or maximum dose 10 mg/kg; followed by continuous infusion</td>
<td>N/A</td>
<td>1.8 to 12 mg/kg/h continuous IV infusion (limit to 5 mg/kg/h for treatment &gt;48 h)</td>
</tr>
<tr>
<td>Remifentanin</td>
<td>5 mg/kg IV (up to 50 mg/min) every 5 min until seizures controlled up to a maximum of 25 mg/kg; followed by continuous infusion</td>
<td>N/A</td>
<td>0.5 to 10 mg/kg/h continuous IV infusion</td>
</tr>
<tr>
<td>Ketamine</td>
<td>1.5 mg/kg IV every 5 min until seizures controlled or up to a maximum dose of 4.5 mg/kg; followed by continuous infusion</td>
<td>N/A</td>
<td>1.2 to 7.5 mg/kg/h continuous IV infusion</td>
</tr>
<tr>
<td><strong>Other potential treatments</strong></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Ketogenic diet</td>
<td>1 g/d for 3 days</td>
<td>N/A</td>
<td>1 mg/kg/d than taper</td>
</tr>
<tr>
<td>Methylprednisolone</td>
<td>0.4-0.6 g/kg/d for 5 days</td>
<td>N/A</td>
<td>N/A</td>
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<tr>
<td>Plasma exchange</td>
<td></td>
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<tr>
<td>Hypothermia</td>
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<tr>
<td>Electroconvulsive therapy</td>
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<tr>
<td>Study</td>
<td>Design</td>
<td>Limitations</td>
<td>Indirectness</td>
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<tr>
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</tr>
<tr>
<td>Rosati et al (2013)</td>
<td>Case Series</td>
<td>Very Serious&lt;sup&gt;a&lt;/sup&gt;</td>
<td>Not Serious</td>
</tr>
<tr>
<td>Synowiec et al (2013)</td>
<td>Case Series</td>
<td>Very Serious&lt;sup&gt;acde&lt;/sup&gt;</td>
<td>Serious&lt;sup&gt;f&lt;/sup&gt;</td>
</tr>
<tr>
<td>Gaspard et al (2015)</td>
<td>Case Series</td>
<td>Very Serious&lt;sup&gt;ade&lt;/sup&gt;</td>
<td>Serious&lt;sup&gt;f&lt;/sup&gt;</td>
</tr>
<tr>
<td>Ilvento et al (2015)</td>
<td>Case Series</td>
<td>Very Serious&lt;sup&gt;a&lt;/sup&gt;</td>
<td>Not Serious</td>
</tr>
</tbody>
</table>

<sup>a</sup> non-blinded, no control group, co-administration of other drugs  
<sup>b</sup> small sample size  
<sup>c</sup> inadequate follow up  
<sup>d</sup> incomplete chart documentation  
<sup>e</sup> variability in timing and dose  
<sup>f</sup> differences in population