Spring 5-19-2023

Managing Refractory Status Epilepticus with Early Ketamine Administration

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MANAGING REFRACTORY STATUS EPILEPTICUS WITH EARLY KETAMINE ADMINISTRATION

A Thesis Presented to
The Faculty of the School of Medicine
Yale University

In Candidacy for the degree of
Master of Medical Science

May 2023

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Table of Contents

List of Tables

List of Abbreviations

SE: Status epilepticus

NCSE: Non-convulsive status epilepticus

RSE: Benzodiazepine-refractory status epilepticus

ABI: Anoxic brain injury

ED: emergency department

AED: antiepileptic drug

SRSE: super-refractory status epilepticus

MAR: medication administration record

EHR: electronic health record

Abstract

Status epilepticus is a time-sensitive neurological emergency that can be associated with severe disability and mortality. Approximately 20% of patients with status epilepticus will fail to respond to existing first and second-line therapies that act on similar receptors. There is a need for additional therapeutic options. One candidate drug, ketamine, has a novel mechanism of action and may work synergistically to terminate seizures. This study seeks to examine whether ketamine administration along with other second-line medications can reduce seizure burden in patients with status epilepticus. Using an open-label randomized clinical trial of 436 patients, we will examine the proportion of patients with decreased seizure burden at 60 minutes after administration when compared to existing, guideline-recommended, first-line therapy. This study seeks to determine whether this new therapeutic strategy for treatment of status epilepticus, via decreased seizure burden, may improve long-term outcomes in this population.

Chapter 1: Introduction

1.1 Background

Status epilepticus (SE) is a relatively common neurological emergency that affects people of all ages.[1] Although approximately 60 people per 100,000 per year will experience convulsive status epilepticus per year, the current treatment regimen is inadequate.[2] As the duration of a seizure event increases, so does the likelihood of increased morbidity. After 30 minutes, the frequency of these adverse outcomes dramatically increases.[3] Morbidity events can include permanent neurologic deficits, though the underlying cause of the seizure can also affect the frequency at which these poor outcomes are noted. Due to prolonged seizures, there is increased metabolic demand and poor mental status leading to an inability to protect the airway. These combined factors can lead to a variety of initial problems including aspiration, rhabdomyolysis, hyperthermia, various electrolyte derangements, and acidosis.[4] As these electrolyte and metabolic abnormalities worsen, cardiac arrhythmias are possible as well as increased strain on the heart. This is particularly problematic for those with poor baseline cardiac function.[5] Despite the dire consequences of failing to terminate seizures, the current treatment algorithm will leave many people seizing after 60 minutes.[6,7] There is a need for new strategies that more effectively terminate SE, decreasing the negative sequelae of these events.

A seizure event is classified as status epilepticus when it lasts greater than five minutes, or if a person experiences two seizures without returning to their baseline level of awareness.[8] Seizures may present as a classic generalized tonic-clonic event or can be focal in nature. The underlying etiology of status epilepticus is diverse and can include individuals who have a history of epilepsy or known structural defect in the brain. Other

etiologies include infections as well as autoimmune or paraneoplastic disorders. At the time of treatment, the exact cause is often not known.[3] Because of the time-sensitive nature of this emergency, treatment must be empirically initiated using a stepwise protocol that does not differentiate based on seizure etiology.

In the treatment algorithm recommended by the 2016 guidelines of the American Epilepsy Society, benzodiazepines are utilized first, followed by a variety of other options if the seizure persists.[7] The choice of benzodiazepine may vary, but intravenous lorazepam or intramuscular midazolam are commonly used.[9,10] If the seizure persists after the first dose, a second dose should be given. In case of complete non-response to benzodiazepines, three common second-line agents are levetiracetam, valproate, or fosphenytoin.[6] Other possible medications are lacosamide, brivaracetam, or phenytoin. Once an individual fails to respond to benzodiazepine therapy, they have less than a 50% chance of seizure cessation after the second-line agent is given.[6,7] Therefore, it is clear based on this effectiveness that there is a need for improved therapies that can more quickly terminate these seizures, potentially leading to improved patient outcomes.

The mechanism of pharmacoresistance in SE has been extensively studied in animal models. There are two main hypothesized physiologic changes that lead to this: increased internalization of $GABA_A$ receptors and externalization of NMDA receptors on the synaptic membrane. As the number of available GABA receptors decreases, the effect of GABA-ergic medications also decreases. Medications that act directly on the GABA receptor include benzodiazepines, barbiturates, and propofol, all of which are commonly used medications in refractory status epilepticus. To counter this effect, some have

suggested using NMDA antagonists in concert with benzodiazepines. This would decrease the global impact of NMDA upregulation and its resulting AMPA upregulation.[11-13]

Ketamine, an NMDA receptor antagonist, has been used in SE treatment since the 1990s but has been typically reserved for cases that persist for greater than 24 hours.[14] Ketamine is commonly used in the emergency department to manage acute agitation and to facilitate procedural sedation.[15] The pharmacokinetic characteristics of ketamine include a half-life of 2-3 hours and drug metabolism by the cytochrome P450 system in the liver. [14] It is generally safe and well-tolerated, especially when compared to many of the other medications used to treat SE. Notably, it does not necessarily require endotracheal intubation, as it does not cause respiratory or cardiac depression.[14,16] When used in combination with other drugs that may cause hypotension, ketamine's sympathomimetic effect may counterbalance and stabilize the blood pressure.[17]. Other well-documented adverse effects are emergence reactions, especially in those with underlying psychiatric illness. In other populations, this is managed by co-administering ketamine with benzodiazepines. Since benzodiazepines would have already been administered as first-line agents in the status epilepticus population, it would be unlikely to see significant rates of re-emergence.[18,19]

1.2 Statement of the Problem

The current standard of care in SE treatment is inadequate as it leaves many patients seizing for greater than 60 minutes. There is a need for new strategies that terminate seizures more quickly. Because ketamine acts on a different pathway than other antiepileptics, it may be able to work synergistically to overcome pharmacoresistance. Prior studies looking at ketamine in SE are limited to case studies and small retrospective

studies that have widely variable populations. Most of these patients had SE refractory to multiple general anesthetics before receiving ketamine, and outcomes were almost universally poor even in those who achieved seizure cessation.[19-21] Because these studies were retrospective, selection bias likely plays a large role in the demonstrated outcomes. To date, there are no prospective studies looking at ketamine use at any point in status epilepticus. There is a signal of benefit, especially when ketamine was given early in the disease course.[16,19] To better understand the actual effect of ketamine used early in SE, higher quality prospective data is needed.

1.3 Goals and Objectives

This study aims to optimize the treatment of benzodiazepine-refractory status epilepticus and increase the proportion of patients who achieve seizure freedom. We plan to investigate the efficacy and safety of ketamine in this population.

1.4 Hypothesis

There will be a significant difference in the proportion of adults who are seizure free at 60 minutes between those who received ketamine for refractory status epilepticus when compared to those who received standard of care. Other secondary outcomes include number and type of adverse events, total hospital and ICU length of stay, intubation rate, mortality, and functional neurological status at 30 days measured with the modified Rankin scale.

1.5 Definitions

- Refractory status epilepticus: status epilepticus that persists despite appropriately dosed benzodiazepine therapy. This term encompasses clinically apparent seizures as well as decreased level of consciousness accompanied by EEG findings consistent with seizure. We did not exclude non-convulsive status epilepticus.

- Standard of care: In this context, the standard of care refers to the clinician's choice of levetiracetam, fosphenytoin, or valproate. Dosing and duration are up to the discretion of the treating provider.
- Adult: individuals aged 18 or older
- Functional neurological status: defined by the modified Rankin scale, administered with standardized interview questions.

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Chapter 2: Literature Review

2.1 Literature Search Criteria

An independent literature review was conducted from June 2022 to May 2023 with assistance from the Yale School of Medicine librarians. This review included multiple databases and was repeated throughout this period to ensure that newly published literature was included. Primary databases used include Ovid, PubMed, Embase, and Scopus. The following key terms were used both independently and in various combinations: *status epilepticus (status, seizure/seizures, epilepsy, drug-resistant epilepsy, super-refractory status, SE, SRSE, RSE, NCSE, CSE), ketamine (s-ketamine, NMDA antagonists), anticonvulsants (antiepileptic drugs, benzodiazepines, levetiracetam, valproate, valproic acid, phenytoin, fosphenytoin), seizure cessation (seizure-free, electrographic seizure cessation).* The largest search parameters are included in the appendix. In addition to database searching, the reference lists of relevant articles were cross-checked for additional resources. Articles were screened by title, abstract, and publication date. Only English-language articles were used. Unless no further evidence was available, only articles published after 2000 were included. Opinion pieces and literature reviews were used in the search process to find additional articles but were not included in the final review. This literature search demonstrates the novelty of our proposal, as no prospective studies examining the use of ketamine early in SE were found. To support the choice of methods and calculation of sample size, studies examining any of the control group medications and primary outcome were also included in the following analysis.

2.2 Mechanism of Pharmacoresistance in Status Epilepticus

The mainstay of the acute and chronic treatment of seizures is GABA receptor modulation. Benzodiazepines increase the frequency of GABA-A channel opening, which

increases influx of chloride into the neurons, hyperpolarizing them and causing an inhibitory effect on action potential conduction.[1] This inhibitory mechanism is the basis for the strong antiepileptic effect of both benzodiazepines and many other antiepileptic drugs used for long-term seizure control. As the duration of status epilepticus (SE) increases, the GABA receptors become internalized within the neurons and are therefore no longer effective drug targets.[2,3] Concurrently, the excitatory NMDA receptors accumulate on the neuronal surfaces.[4-7] As a seizure continues, the concentration of excitatory neurotransmitters increases, causing additional activation and prolongation of the seizure.[8] This model is called the receptor trafficking hypothesis, and explains the clinical observations that seizures become more difficult to terminate as duration increases.[6,9,10] Ketamine is an NMDA receptor antagonist that theoretically decreases neuroexcitation and can lead to seizure termination given these physiologic changes.[11,12] This data is from animal studies, but it provides a rationale for why combinations of benzodiazepines, non-benzodiazepine GABA-modulating drugs, and ketamine may work synergistically to terminate refractory SE by targeting different receptor groups.[13-18]

2.3 Trends in Ketamine Literature

Although no prospective data exists on this topic, several centers have reported their experience using ketamine in refractory SE. Because of the retrospective nature of this data and wide practice pattern variations, the affected population, route, dose, and timing of administration also vary widely. In general, most patients received ketamine quite late in their disease course after many other medications had been tried, often several days after seizure onset.[19-21] Several studies included participants of any age[22,23], while others focused on either children[19,24,25] or adults.[20,21,26-34] Because seizure etiology is often unclear at presentation, there is no etiologic-specific grouping of patients in these retrospective

reports. This is significantly problematic given that, in general, those with pre-existing epilepsy have higher rates of seizure cessation in status overall when compared to those with other etiologies including anoxic brain injuries or CNS infection, which tend to be more refractory.[23]

Even within a single study, dosing variation is broad. Most individuals received a loading dose followed by an IV infusion, although some received an infusion alone. [23,26,27,35] Srivinas et al found that the use of a loading dose was not associated with seizure cessation, however this conclusion may have been biased since those included in the loading dose cohort were overall of higher acuity and a high proportion of this group had anoxic brain injury.[23] Since the majority of these patients received IV ketamine multiple days after seizure onset, they had received a wide variety of medications before the ketamine. Most were intubated, although Ilvento et al administered ketamine before intubation and were able to avoid this outcome in 80% of these children.[24]

2.4 Potential Benefits to Ketamine Administration

In addition to its utility in terminating seizures, ketamine may also improve clinical outcomes by avoiding intubation, providing neuroprotection in extended SE, and decreasing vasopressor requirements. In contrast to other medication choices for refractory status such as propofol, phenobarbital, and midazolam, ketamine does not directly cause respiratory depression.[36] It is frequently used for procedural sedation because respiratory drive is better preserved compared to using propofol or other anesthetics.[37] Administering ketamine early in the clinical course could prevent progression to intubation and subsequent negative complications. This has been poorly studied, as ketamine has historically been given only as the last resort. Ilvento et al found that 80% of children who

received early ketamine while in SE were able to avoid intubation (4/5 children).[24] Additionally, ketamine may have neuroprotective effects. It is well-established that longer seizure duration is associated with worse neurological outcomes, as previously discussed.[38-40] In several animal models, ketamine administration is linked to fewer neurologic deficits even when seizure duration is held constant.[14,15,41 42] This effect is more pronounced when ketamine was administered alongside benzodiazepines, but the mechanism of this effect remains unclear.[14]

Hypotension is a common concern in patients in RSE who require anesthetic agents. Patients commonly require one or more vasopressors to maintain adequate perfusion while undergoing treatment for RSE.[43] However, unlike other anesthetics, ketamine typically is associated with hypertension, which can be advantageous in this patient population. The increase in blood pressure occurs primarily via peripheral vasoconstriction, with some minor increases from tachycardia.[7] In several studies, the need for vasopressors was decreased or even eliminated following ketamine administration.[20,22-26,32,44] Ketamine theoretically will promote hemodynamic stability and decrease the need for vasopressor support and the side effects that accompany them. However, one important limitation is in those patients with severe cardiovascular disease who may not tolerate the relative tachycardia and increase in blood pressure.[40]

2.5 Barriers to Ketamine Use

Ketamine has been studied in status epilepticus for several decades yet remains rarely used for this indication, despite being an approved medication on many institutional protocols. Several barriers may decrease the likelihood that a provider will use this medication.[45] First, there is a widely-held belief that ketamine can increase intracranial

pressure (ICP).[26,40] This belief came from a series of small trials in which patients received nonstandard anesthetic dosing regimens.[26] However, this finding has not been replicated outside of these trials with mounting evidence suggesting ICP does not change with ketamine use. But, despite the minimal evidence, a warning for increased ICP has deterred physicians from prescribing ketamine in their neurologic patients.[45] Zeiler et al conducted a systematic review of the literature in patients without underlying trauma. They found no association with increased intracranial pressure when ketamine was given in bolus or continuous dosing. There was a mild increase in cerebral perfusion pressure and decrease in vasopressor requirements.[46] The only adverse events noted across these studies was some transient tachycardia.

Another concern is emergence, the phenomenon where individuals can experience psychiatric distress and agitation when waking up after ketamine administration. Individuals that receive ketamine for pain control are more likely to report hallucinations or vivid dreams compared to those that receive a different medication.[47] History of psychosis is not a contraindication to receiving ketamine, and there is no evidence to suggest increased risk of emergence in those with comorbid psychiatric illness.[48] Emergence phenomena are unlikely to occur in the SE patient due to the concurrent administration of benzodiazepines.[44] Both the anesthesia and the emergency medicine literature report that emergence phenomena are uncommon when ketamine is given alongside benzodiazepines.[49,50]

Another challenge in both conducting research and incorporating ketamine into clinical practice is the variability in seizure management between centers and clinicians. For example, benzodiazepines have been recommended as first-line therapy for SE for

many years. [51-54] Despite this, many individuals in status epilepticus receive either inadequate doses of benzodiazepines or no benzodiazepines at all. Ferlisi et al gathered data from physicians and other providers in several countries from 2013-2015 and found that only 33% of individuals with status epilepticus received benzodiazepines as their first-line therapy.[55] Even within the US, many patients receive inadequate doses. In the ESETT trial, the landmark trial comparing levetiracetam, fosphenytoin, and valproate, most participants did not receive the guideline-recommended dose of either lorazepam or midazolam.[56] Despite this underdosing, individuals who received target range doses did not have better outcomes or a higher proportion who achieved seizure cessation. However, this underlines how difficult changing established clinical practice can be, especially in emergencies where clinicians often draw from experience rather than guidelines. Kellinghaus et al looked at factors associated with cessation of status epilepticus in Germany, Austria, and Switzerland, and found a similar trend of underdosing benzodiazepines.[57]

Conducting research in individuals with status epilepticus is also challenging. SE is a relatively rare disease, and refractory SE is even more rare.[52,58,59] Given the low incidence, trials can often require long recruitment periods, unless a multitude of centers are participating. This difficulty is not unique to ketamine; other antiepileptic drugs are supported by mostly retrospective data. Even when prospective trials are successful, they are often stopped early due to nonsignificant outcomes.[56] The study design itself is also challenging because individuals are not able to consent prior to enrollment, which necessitates an application for an exception to informed consent (EFIC) from the FDA. This process will delay approval and increase the cost of the study. It is much simpler to

do retrospective research in this population. Another challenge is the multiple specialties that need to work together to successfully complete prospective research. Although neurology providers take care of these patients throughout their course, emergency department providers are the first to encounter them. A successful protocol starts in the ED or even prior to arrival and must continue once in the inpatient setting. Practice patterns and protocols may vary significantly between these groups, especially in a multi-center study. A successful project will need to involve stakeholders from each group to collaboratively put together a feasible plan.

2.6 Safety and Adverse Events

Each of the drugs used to treat refractory status epilepticus has its own profile of adverse events. Selection depends on individual patient risk factors, availability, and clinician preference. The most commonly referenced medications in this population are valproic acid, levetiracetam, fosphenytoin, and lacosamide.[60] Since ketamine is an well-studied drug with multiple uses, its relevant adverse effects and side effects are also well-documented. Valproate lacks significant cardiotoxicity or hypotension risk, but can cause hyperammonemia, hepatic dysfunction, pancreatic pathology, and abnormal bleeding.[60,61] In general, these effects are transient and well-tolerated. Use of this medication chronically is associated with more significant liver abnormalities.[62] Valproate is a cytochrome P450 inhibitor and interacts with many other medications. [43]Levetiracetam, and its newer analog brivaracetam, has few side effects and does not interact with most other medications. It is unlikely to cause hemodynamic instability or cardiovascular effects.[60,63,64] Phenytoin and fosphenytoin (more readily available in the US) are older medications that have significant cardiac side effects including arrhythmias, hypotension, and decreased cardiac output.[60] They are also associated with respiratory depression.[56,64] Lacosamide is a newer agent that

has relatively few adverse events, but occasionally can cause various arrhythmias, PR prolongation and heart block.[60,65]

2.7 Possible Confounding Variables

Confounders that may have affected prior studies include seizure etiology, age and other comorbidities, and time to antiepileptic drug administration. Randomization as planned in this study should help decrease these effects. Etiology may be linked to ketamine administration, as certain causes of SE are more likely to be refractory. In current practice, most people only receive ketamine after several other drugs have failed. This subtype of patient is sometimes called super-refractory status epilepticus (SRSE) and has a high mortality rate of 30-50%.[66,67] Achieving seizure cessation by any means is difficult in this population, and may not reflect ketamine's true efficacy in a broader population.[68] Another challenge in interpreting this data is time to drug administration. Most protocols and national guidelines recommend administering the initial benzodiazepines approximately 5 minutes after seizure onset.[52,69] In many locations, EMS services are not available in that timeframe and treatment will be delayed.

2.8 Methodology in the Literature

2.8.1 Variables and Outcomes

We chose our variables for this study based on prior reporting, although outcomes vary widely between studies. Most of the prior literature using ketamine in SE administered the drug much later in the disease course, so the outcomes were not relevant to the early management of SE. For example, Alkhachroum et al, one of the largest studies of ketamine in SE, used an outcome of electroencephalographic seizure control or 50% reduction in seizure burden at 24 hours after ketamine administration.[26] Another of the larger trials, Höfler et al, measured seizure control at 72 hours after ketamine administration.[30] These

time points are relevant once the patient has reached super-refractory status, but are not appropriate for early management. We propose adding ketamine to the treatment regimen before any other anesthetic drugs are administered and alongside antiepileptic drugs like levetiracetam, fosphenytoin, or valproate. Various protocols have been proposed, but most experts and guidelines suggest administering second-line agents at approximately 30 minutes from seizure onset (provided adequate benzodiazepine dose has already been given).[40,43,70] If the seizure persists after 60 minutes from AED administration, most protocols move on to intubation and anesthetic medications.

We chose our primary outcome (seizure cessation at 60 minutes following ketamine administration) to more easily compare to other trials looking at effectiveness of other second-line medications in SE. The ESETT trial used a similar, composite outcome that included either clinical seizure cessation or improvement in level of consciousness at 60 minutes.[56] Other trials track seizure cessation at any time point after administration of the study drug[71], or seizure control without recurrence in the 1st 24 hours.[72] Klowak et al performed a meta-analysis of AED effectiveness in children and reported seizure cessation at both 20-40 minutes and 1-3 hours.[64] Other studies analyzing the effect of these drugs in SE did not include time in the primary outcome, choosing instead to focus on EEG findings, need for additional medications, or long-term neurological function.[63,73-75] Given the wide variety of primary outcomes, we chose to use seizure cessation at 60 minutes from drug administration to more closely approximate the time limits recommended in the guidelines.

Dose selection was also widely variable between the ketamine studies. In the table below, median and range of doses used in various studies are shown, as well as whether patients received a loading dose. We elected to use a loading dose of 1.5 mg/kg

administered as an IV push, with reloading of 0.5 mg/kg IV every five minutes. All doses are calculated using actual body weight as opposed to ideal body weight. The maximum total loading dose is 4.5 mg/kg actual body weight. The patient would then be transitioned to a maintenance infusion of ketamine. This dosing strategy involves faster titration than several of the other studies, primarily because it is administered much earlier in the disease course.

Table 1: Ketamine Dose Trends

First author, year	**Dose (mg/kg/h)**	**Loading dose**
Alkhachroum, 2020	2.2 (+/- 1.8) Mean (+/- SD)	None
Basha, 2015	3 (+/-1.6) Mean (+/- SD)	4/11 patients, 1.1-4 mg/kg
Caranzano, 2022	5 (2.5-15) Median (range	None
Hofler, 2016	2.4 (1.5-3.0) Median (IQR)	7/42 patients, 200 mg (200-250) Median (IQR)
Gaspard, 2013	2.75 (0.05-10) Median (range)	All, 1.5 mg/kg (5 mg/kg) Median (maximum)
Sabharwal, 2015	1.5-10.5 Range	None
Synowiec, 2013	1.2 (+/-0.6) Mean (+/-SD)	All, median 1.0 mg/kg
Dericioglu, 2021	1-5 Range	All, 0.5-2 mg/kg
Ilvento, 2015	1.8 (0.42-3.6) Median (range)	All, 2 boluses 2-3 mg/kg q5 minutes
Rosati, 2012	2.4 (0.6-3.6) Median (range)	All, 2 boluses 2-3 mg/kg q5 minutes
Srinivas, 2022	2.43 (5.55) Median (maximum)	50%, 2 mg/kg (10 mg/kg) Median (maximum)

2.8.2 Randomization and Blinding

None of the studies looking specifically at ketamine in status epilepticus were randomized or blinded. Since all the data is retrospective and observational, medication regimens were entirely at the discretion of the treatment team. In addition, none of the prior literature included control or comparison groups. With a few exceptions,[55,76,77] these studies did not blind the outcome assessors since no comparison was being made. In the broader SE literature, most trials did not blind clinicians to which drug a patient was

receiving.[62,63,71-75,78-87] Patients in either convulsive or nonconvulsive status epilepticus would have all had a decreased level of awareness and so could not be considered formally blinded. Several trials used identical syringes/study drug delivery devices to blind clinicians to which intervention a patient had been randomized.[51,56,88-93] These studies compared a variety of medications and time points to control SE. The ketamine literature is limited by its lack of blinding and introduces observer bias. The planned study is open-label to decrease barriers to enrollment and overall cost. This is congruent with most of the existing SE literature which is routinely used to guide management. All outcome assessors will be blinded.

So far, none of the ketamine literature in this population randomized participants to treatment or comparator groups. Randomization will decrease the impact of selection bias and ensure that the two groups are similar in baseline characteristics. The prospective randomized trials that guide SE treatment protocols used a variety of randomization strategies. Kapur et al and Silbergleit et al utilized an age-stratified "use-next" medication box in the treatment areas that had been previously randomized with a computer-based random number generator.[51,56] They also had study mobile devices that notified the appropriate teams, gave medication instructions, and recorded administration times. Amiri-Nikpour et al used a block randomization strategy.[79] In this type of randomization, participants are divided into equally sized groups, then randomly allocated between the available treatment arms. This strategy results in more uniformly distributed groups when compared to simple randomization.[94] Dalziel et al also used block randomization, but further stratified by age.[63] Chakravarthi et al and Misra et al used simple sequential randomization (odd- and even-numbered study participants received two different

interventions).[74,80] Each of these methods could yield random groups with balanced baseline characteristics. Because of the time constraints of this study, rapid assignment to the correct group is paramount for success. We chose to use block randomization with a mobile study device present at each site to minimize delays in treatment.

2.8.3 Selection and Exclusion Criteria

In table 2, we present a list of exclusion criteria which are planned for this research. We elected to keep our list of exclusion criteria to a minimum to ensure the results are applicable to a broad range of individuals suffering from status epilepticus. The existing ketamine literature does not report any consistent criteria, as it was entirely up to clinician discretion. We modeled our selection criteria on the prospective trials in this population using different interventions.

Table 2: Exclusion Criteria

Common exclusion criteria	**Other exclusions**
• Major trauma • Hypoglycemia • Cardiac arrest/severe hemodynamic instability • Need for urgent neurosurgical intervention • Known allergy to study drug • Prior opt out (medical alert bracelet)[95] • Received inadequate benzodiazepine dose[56,62] • Patients intubated prior to enrollment[56,82]	• Age >18 years[95] • Age <16 years[57] • Age <2 years[96] • No prior diagnosis of epilepsy[96] • Known anoxic brain injury[91] • Known pregnancy[91] • Significant rhabdomyolysis[91] • Known CNS malignancy[87] • Nonconvulsive status[84,86] • Hepatic or renal failure[86] • Known pancreatitis[61] • History of severe coronary artery disease with decreased ejection fraction[83] • Current arrhythmia[72] • Suspected psychogenic non-epileptic activity[72,90]

2.8.4 Follow-up

Because SE is an acute and time-limited disease state, most adverse effects from either the seizure itself or the medications used to treat it should be seen shortly after the event. Ketamine and other anesthetics used to treat SE are also not used long term, in

contrast to the antiepileptic drugs. Most of the ketamine-specific literature reported safety data during hospitalization, and some followed the patients for weeks to months after discharge. Höfler et al reported outcomes for 12 months following hospital discharge, the longest frame among this group.[30] Talahma et al published a case report of a single pregnant patient who received ketamine, and reported progress up to 10 months after seizure onset.[33] The majority of these studies reported data only until hospital discharge. To maximize number of subjects recruited during the study period, we chose to report safety data, mortality, and neurological functional status up to 30 days after randomization.

2.8.5 Statistical Analysis

Statistical analysis test selection was informed by the other prospective experimental trials in this population. Because the primary outcome varied between each trial, the analysis was similarly diverse. For categorical variables, most studies used Fisher's exact test.[72,80] Dichotomous variables were assessed using chi-square test.[56,63,72,88,90] Continuous variables were assessed using the Mann-Whitney U test[79,80,83,85] or t test.[63,72] Masapu et al also utilized a Kaplan-Meier curve to describe time to drug cessation.[83]

2.8.6 Sample Size Calculation

As there is no prospective literature currently available evaluating ketamine in this population, no formal sample size calculations are available for comparison. Instead, effect size for both intervention and comparison groups were extrapolated from related studies. The comparison group effect size was obtained from the ESETT trial.[56] The primary outcome used in this trial is similar to the proposed outcome for our study and was used directly in the sample size population. Although this RCT was large and well-conducted, it was stopped early due to a planned interim analysis that showed less than 2% chance of

statistical significance. The intervention group effect size was derived from two studies. The first (Alkhachroum et al 2020) was selected because the population was most similar to our target population.[26] Compared to all other studies that used ketamine in SE, participants received ketamine much earlier (many within hours of symptom onset). This was also the largest sample size in the group of ketamine studies (n=68) and looked at only adults. The effect size was 81% seizure control at 24 hours. Because of the difference in time course for the proposed primary outcome, an additional study was used to adjust the effect size. Published in 2022, Jacobwitz et al examined the use of ketamine to treat RSE in a pediatric population.[97] Their primary outcome was also seizure cessation at 24 hours, but they also included interim time points to evaluate ketamine's speed of onset. In this group, 75% of those who ultimately responded to ketamine did so within the first 60 minutes. The primary limitation of this data is the population; no one over age 18 was included. Using this additional data, we adjusted the proposed effect size down by 25%, for a final intervention group effect size of 60%.

Table 3: Sample Size

Author, year	**Study Design**	**Outcome Operationalization**	**Used for**	**Effect Size**	**Limitations**
Kapur, 2019	RCT	Composite primary outcome: improvement in level of consciousness or electrographic seizure cessation at 60 minutes (dichotomous)	Comparison group effect size	46% achieved primary outcome	Composite variable, trial stopped early
Alkhachroum, 2020	Descriptive observational	Electrographic seizure control at 24 hours (dichotomous)	Intervention group effect size	81% achieved primary outcome	Descriptive study design with heterogenous groups, different time point with no data available at 60-minute mark

Jacobwitz, 2022	Retrospective cohort	Seizure cessation at 24 hours, includes time point data	Intervention group effect size, clarify time course	75% of ketamine responders had seizure cessation in first 6 hours	Study in children, not adults. Retrospective study with heterogenous groups

Based on the literature previously described, the anticipated effect size is 14%. Using an alpha of 0.050, desired power of 0.80, and a two-tailed hypothesis, the required sample size is 398 (199 per treatment arm). Losses to follow up are expected to be minimal given the short duration, but we expect that some individuals will choose to withdraw their data from the study. After adding 10% to the sample sizes, the recruitment target is 218 individuals per group with a total of 436. For the given effect size, sample sizes and alpha, power is 0.801, indicating that 80% of studies would be expected to yield a significant effect.

2.9 Strengths and Weaknesses

Although limited by their size and observational designs, the ketamine literature provides valuable information about a difficult to study population. Benzodiazepine-refractory SE is rare, and many centers do not have much experience caring for these individuals. Successful prospective research will require multi-center participation and well-defined protocols. The literature base includes data from many different countries and highlights the differences between healthcare systems in each region. This diversity increases the external validity of the findings and means that a broad population of individuals who experience SE are represented. In addition, decades of research have increased our understanding of the mechanism of benzodiazepine resistance in SE in animal models.

The largest weakness of the ketamine literature is its retrospective nature. Because there are no comparison groups, randomization, or blinding, clinician bias likely has a large effect on the outcomes of these trials. Patients that receive ketamine are highly selected, often as the sickest patients within the broader SE population. This may actually cause ketamine's true effect to be under-reported. Conversely, clinicians that are excited about the prospect of using ketamine to treat SE may select patients that they feel are likely to recover. It is difficult to draw any solid conclusions about long-term survival and patient-centered outcomes following ketamine administration. This study will fill a much-needed void in the ketamine literature and provide more reliable data on its efficacy. This will inform future guidelines and shape clinician management in this vulnerable population.

2.8 References

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Chapter 3: Methods

3.1 Study Design

This is a multi-center, open-label parallel randomized controlled trial. Study sites include multiple emergency departments in the Yale New Haven Health (YNHH) system.

3.2 Study Population and Sampling

The source population for both the intervention and control groups are adults, individuals 18 years or older, with or without a history of epilepsy that present in status epilepticus that is refractory to benzodiazepine therapy. Subjects for both groups are sampled from individuals presenting to a YNHH emergency department. The exclusion criteria are kept deliberately minimal to allow results to be broadly applicable. Subjects are not excluded based on seizure etiology, known toxicologic exposure, or prior history of seizures or SE. Exclusion criteria are presented below in Table 4.

Table 4: Exclusion Criteria

Exclusion	**Operationalized**	**Purpose**
Known pregnancy	Based on history and/or physical exam	Protected population
Prisoner	Anyone in police custody or guarded at time of enrollment	Protected population
Opted-out ID band	All subjects will be checked for obvious medical alert bracelets/jewelry at time of enrollment	Part of exception from informed consent (EFIC) requirements
Treatment with general anesthetics (ex: propofol, etomidate, barbiturates)	Documented in MAR	Prevent confounding
Cardiac arrest prior to receiving study drug	Based on clinical context	Prioritize ACLS
Known allergy to study medications	Based on history or medical alert jewelry	Prevent harm
Hypoglycemia <50 mg/dL	All participants will be screened with POC blood glucose at enrollment	Prioritize correcting hypoglycemia

3.3 Subject Protection and Confidentiality

IRB approval: IRB approval will be obtained following Yale University's prespecified guidelines. The project advisor meets the IRB requirement for principal investigator. The

student investigator has completed human subject protection training before requesting project approval.

Funding: Funding is not required in the scope of the project. Possible sources include university or health system grants.

Consent: This project requires emergency exception from informed consent (EFIC) as allowed by the FDA. This includes additional approval prior to beginning recruitment. Individuals have the right to withdraw from the study at any point if they regain consciousness. We will conduct community meetings to inform the public of this study, as well as to give individuals the right to opt out with medical alert bracelets. See the appendices for complete details.

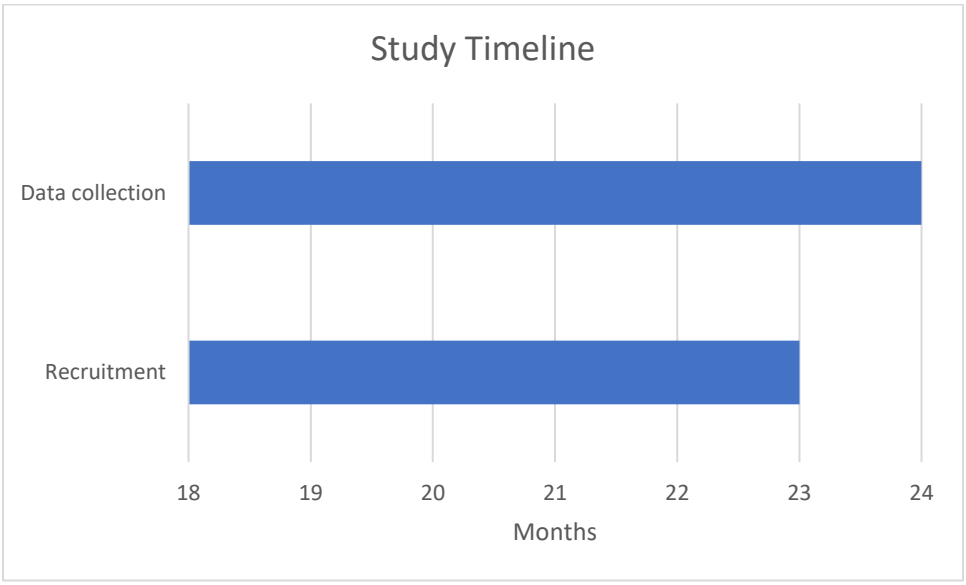
Special populations: This study does not include children, known pregnant individuals, prisoners, or other protected populations.

Confidentiality and HIPAA: All individuals with access to protected health information will have completed annual HIPAA training and are subject to Yale University oversight. The number of individuals with access to this information is minimized to decrease exposure. All records must be kept on secured, university-owned devices and transmitted using encrypted file transfer services. Records will be deidentified prior to assessor review.

3.4 Recruitment and Timeline

Subjects will be enrolled in the study from the emergency departments of multiple YNHH facilities (Yale New Haven Hospital, Bridgeport Hospital, Greenwich Hospital, Lawrence + Memorial Hospital, and Westerly Hospital). All ED physicians/advanced practice providers and neurology staff at participating facilities will be provided with study

details and training sessions. Although this study is coordinated by the neurology department at YNHH, we recognize that ED staff are likely to administer second line treatment (the study drug or standard of care) before neurology arrives. ED staff is therefore responsible for enrolling patients in the trial. If the patient regains consciousness at any point during their hospital stay, neurology staff will be responsible for consenting them. Study participants will be recruited during the first 23 months of the trial period and follow up will continue for one month after enrollment.



3.5 Study Variables and Measures

The primary outcome (dependent variable) is the number of subjects who are no longer seizing at 60 minutes after benzodiazepine administration. This time point was selected to reflect the fact that many seizures begin unwitnessed. Using an outcome of time from seizure onset would exclude those individuals, who may represent a different population. We chose to use a dichotomous variable as the primary outcome versus time to event because most other studies conducted in status epilepticus use similar variables. Using the same outcome will allow better comparison with other trials. Seizure cessation

is defined as either improvement in level of consciousness or decrease in seizure burden on EEG. Either ED or neurology providers are responsible for documenting seizure cessation at the 60-minute time point. EEG data will be obtained using point of care rapid EEG devices or formal EEG recordings, whichever is more rapidly available. The point of care devices will be stocked in each participating ED along with the study mobile device. EEG data is recorded and stored for future review.

The intervention (independent variable) is the administration of ketamine after initial treatment with benzodiazepines fails. Ketamine is administered at least 5 minutes after the second dose of benzodiazepines as a loading dose (1.5 mg/kg IV push). The subject can be reloaded every 5 minutes as needed with an additional 0.5 mg/kg each time. The maximum total loading dose is 4.5 mg/kg actual body weight. At this point, they would be transitioned to a maintenance infusion of ketamine. This intervention does not preclude the administration of other antiepileptic drugs, as they would now qualify for them based on their history of status. The administration of the initial loading dose and subsequent titration will be recorded in the medication administration record by nursing staff and extracted by study personnel. The comparator group is the standard of care/clinician choice per the YNHH SE protocol. This could include levetiracetam, fosphenytoin, or valproic acid. The medication choice and administration time will be extracted from the MAR by study personnel.

Secondary outcomes

- Functional neurological status at 30 days (modified Rankin scale): The modified Rankin scale (mRS) is the most utilized functional assessment in patients who have suffered a neurological insult. It is measured by a clinician

either while inpatient or over the phone using the standardized structured interview.[1] If the subject is unable to complete the interview, family or caregiver information will be used. The scoring system and standardized interview template can be found in the appendix.[2,3]

- All-cause mortality at 30 days: Study personnel will review the electronic health record (EHR) to determine if each subject survived to 30 days after trial enrollment. If unclear, they will contact the subject/family to confirm.
- Intubation: All trial participants will be assessed for intubation at any point during their hospital admission. This is a dichotomous variable and will be obtained from EHR.
- Length of stay: Study personnel will extract this information from the EHR. This metric includes only the initial hospitalization, not any readmissions that might occur during the 30-day follow-up period. This will include deceased patients, reported as the length of stay at the time of death. If participants are still admitted to a hospital facility 30 days after enrollment, they will be reported in the ≥ 30 days category.

Table 5: Outcomes

Outcome	**Operationalization**	**Reported As**	**Statistical Analysis**
Primary: Seizure cessation at 60 minutes	Dichotomous	N (%)	Chi-square
Intubation	Dichotomous	N (%)	Chi-square
mRankin score at discharge	Continuous	Median (IQR)	Mann-Whitney U
All-cause mortality at 30 days	Dichotomous	N (%)	Chi-square
Length of Stay	Continuous	Median (IQR)	Mann-Whitney U

3.6 Follow-up and Temporality

Participants will be followed while inpatient by study personnel. All documentation while admitted will be reviewed in the EHR. At 30 days, researchers will document all-cause mortality and mRS. Given the short half-life of all medications involved, any adverse events would be anticipated to occur during or shortly after administration.

3.7 Randomization, Blinding, Adherence, and Monitoring

Randomization: We plan to utilize block randomization across all sites. A study device (mobile phone) is present in each emergency department within the medication room. This can be quickly accessed to determine whether participants are randomized to the ketamine group or the usual care group. The study device also provides drug administration instructions to standardize the intervention.

Blinding: Clinicians and participants are not blinded due to logistical constraints and characteristic side effects of the study drug (namely, hypertension immediately after administration). Participants are expected to have an altered level of consciousness during the administration. Assessors will be blinded to treatment arms.

Adherence: All medication is to be administered by healthcare workers, not participants. The time, dose, and route of each medication are documented in the MAR.

Monitoring: Significant adverse events will be monitored and recorded by nursing staff. See table below for parameters/definitions.

Table 6: Adverse Events

Event (within 60 minutes of administration)	**Parameters**
Hypotension	MAP <65 for greater than 5 minutes
Cardiac arrhythmia	New atrial fibrillation, atrial flutter, ventricular tachycardia, ventricular fibrillation, AV block
Anaphylaxis	NIAID/FAAN criteria for anaphylaxis[4]
Respiratory depression	Respiratory rate <10
Emergence phenomena	Acute psychosis or hallucinations
Hepatic transaminitis	Acute elevation in AST or ALT

3.8 Data Collection

Study personnel will be notified each time an individual is enrolled in the study. The intervention and all subsequent data will be entered into the EHR and can be reviewed at a later date. The mRankin score and standardized interview (administered 30 days after enrollment) can be found in the appendix.

3.9 Sample Size

Based on the literature previously described, the anticipated effect size is 14%. Using an alpha of 0.050, desired power of 0.80, and a two-tailed hypothesis, the required sample size is 398 (199 per treatment arm). Losses to follow-up are expected to be minimal given the short duration, but we expect that some individuals will choose to withdraw their data from the study. After adding 10% to the sample sizes, the recruitment target is 218 individuals per group with a total of 436. For the given effect size, sample sizes, and alpha, power is 0.801, indicating that 80% of studies would be expected to yield a significant effect. See the appendix for further details on this calculation.

Per year, there are approximately 60 cases of status epilepticus per 100,000 individuals.[5,6] Per the 2021 US census, there are 3.6 million residents of Connecticut, so approximately 2100 cases of convulsive SE per year. Conservatively, about half of these individuals will present to YNHH hospitals. Approximately 55% of individuals will respond to initial benzodiazepine therapy and return to their baseline.[7] We expect to see

approximately 475 individuals per year within the YNHH system that are refractory to benzodiazepine therapy. This sample size target is reasonable given the size of the healthcare system and the incidence of the disease.

3.10 Analysis

Patients enrolled will be assessed using the descriptive variables described below. The primary outcome is dichotomous and will be compared using a chi-square test. The outcome will be listed as N (%). The secondary outcomes include intubation, modified Rankin scale, and all-cause mortality at 30 days. The modified Rankin output is continuous and will be compared using the Mann-Whitney U test. Intubation and mortality are dichotomous and will be compared using chi-square.

Table 7: Population Descriptive Variables

Characteristic	Ketamine Group	SoC group	Statistical test
Age (quant parametric)	Mean (SD)	Mean (SD)	Student t-test
Sex assigned at birth (categorical)	N (%)	N (%)	Chi-square test
# prior SE episodes (quant non-parametric)	Median (IQR)	Median (IQR)	Mann-Whitney U
Etiology (categorical)	N (%)	N (%)	Chi-square test
On prior AED (dichotomous)	N (%)	N (%)	Chi-square test
Time from onset to benzodiazepine administration (quant non-parametric)	Median (IQR)	Median (IQR)	Mann-Whitney U
Time from onset to ketamine administration (quant non-parametric)	Median (IQR)	Median (IQR)	Mann-Whitney U
Seizure type: NCSE vs CSE (categorical)	N (%)	N (%)	Chi-square test
Prior mRankin (quant non-parametric)	Median (IQR)	Median (IQR)	Mann-Whitney U

3.11 References

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Chapter 4: Conclusion

4.1 Advantages and Disadvantages

Ketamine has the potential to terminate seizures that are unresponsive to first-line benzodiazepines, thereby decreasing adverse neurological outcomes for patients. It may also prevent progression to invasive ventilation, which has traditionally been necessary in these refractory cases. It is safe and well-tolerated in most individuals and can decrease the need for vasopressor support by increasing the cardiac output. Our current standard of care leaves many patients seizing at the 60-minute mark, and many progress to super-refractory SE. This study will provide a solid evidence base to guide clinician choice in this challenging population.

We selected a randomized, open-label study design to decrease the impact of selection and awareness biases. Although clinicians will not be blinded, the participants themselves will be unaware of their study arm assignment and outcome assessors will also be blinded. Patients will be block-randomized across multiple hospitals within the same system, and successful randomization will be confirmed by measuring baseline descriptive statistics. If needed, logistic regression will be used to minimize confounding. This randomization strategy will mitigate the impact of selection bias and increase the internal validity of the study.

The primary outcome was selected to closely align with other landmark studies in status epilepticus. Although not designed to compare ketamine head-to-head with any single other treatment, we hope to show that adding ketamine to the regimen will increase the proportion of individuals who are seizure-free at 60 minutes. We also chose to include

patient-centered outcomes (mortality, intubation, neurologic function) as part of our analysis. By including patients from multiple emergency departments in urban and suburban centers, we hope to capture a diverse range of patient experiences. The proposed sample size (436 total patients) is feasible across the two-year recruitment period. All study medications are readily available within all the emergency departments that will be enrolling patients.

Although this study seeks to provide information about intubation rates, mortality, and neurological outcomes, it is not powered to make causal conclusions about these topics. Rather, we hope to determine ketamine's effectiveness conclusively when used early in status epilepticus. The secondary outcomes will provide support for future studies that more specifically examine these outcomes and compare them head-to-head. Another limitation is the length of follow up. Due to time and funding constraints, we were unable to follow individuals for a 12 month or greater period. This long-term data would provide more details on neurological outcomes, which are often what matters most to our patients.

4.2 Clinical Significance

Management of status epilepticus once refractory to benzodiazepines is mostly an evidence-free zone, with national guidelines leaving the decision up to the individual clinicians.[1] Completion of this study will provide new insight into a promising medication and lay the foundation for future prospective research. With better data, guidelines can be created that decrease practice variation and ensure all patients receive optimal care. More aggressive early management of SE could help terminate seizures sooner, leading to better neurological outcomes and decreased disability.[2] Because ketamine is a medication already carried by EMS agencies, they would be able to easily add it to their protocols for SE. For

rural areas and small emergencies departments, using ketamine could decrease the number of patients who require invasive mechanical support. These critically ill patients are resource-intensive and may stretch the limits of these settings. Stabilizing them early without the need for intubation could benefit the system as a whole and improve outcomes for all patients in that setting.

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Appendices

Appendix A: Ovid Search Parameters

Table 8: Search Parameters

Set	Search Statement
1	exp Status Epilepticus/
2	seizure.mp. or exp Seizures/
3	status epilepticus.mp.
4	exp Epilepsy/ or exp Drug Resistant Epilepsy/ or epilepsy.mp.
5	super-refractory status.mp.
6	1 or 2 or 3 or 4 or 5
7	ketamine.mp or exp Ketamine/
8	NMDA antagonist.mp.
9	s-ketamine.mp.
10	7 or 8 or 9
11	anticonvulsant.mp. or exp Anticonvulsants/
12	benzodiazepines.mp. or exp Benzodiazepines/
13	antiepileptic drugs.mp or exp Anticonvulsants
14	levetiracetam.mp or exp Levetiracetam/
15	valproate.mp. or exp Valproic Acid/
16	phenytoin.mp. or exp Phenytoin/
17	fosphenytoin.mp.
18	11 or 12 or 13 or 14 or 15 or 16 or 17
19	exp Humans/
20	6 and 10 and 18 and 19

Appendix B: Data Collection and Measurement Instruments

Modified Rankin Scale and Standardized Interview:

The Modified Rankin Scale and Corresponding Sections of the Structured Interview

Modified Rankin Scale[3]	Structured Interview for the Modified Rankin Scale
5=Severe disability: bedridden, incontinent, and requiring constant nursing care and attention.	5=Severe disability; someone needs to be available at all times; care may be provided by either a trained or an untrained caregiver. Question: Does the person require constant care?
4=Moderately severe disability: unable to walk without assistance, and unable to attend to own bodily needs without assistance.	4=Moderately severe disability; need for assistance with some basic ADL, but not requiring constant care. Question: Is assistance essential for eating, using the toilet, daily hygiene, or walking?
3=Moderate disability; requiring some help, but able to walk without assistance.	3=Moderate disability; need for assistance with some instrumental ADL but not basic ADL. Question: Is assistance essential for preparing a simple meal, doing household chores, looking after money, shopping, or traveling locally?
2=Slight disability; unable to carry out all previous activities but able to look after own affairs without assistance.	2=Slight disability; limitations in participation in usual social roles, but independent for ADL. Questions: Has there been a change in the person's ability to work or look after others if these were roles before stroke? Has there been a change in the person's ability to participate in previous social and leisure activities? Has the person had problems with relationships or become isolated?
1=No significant disability despite symptoms; able to carry out all usual duties and activities.	1=No significant disability; symptoms present but not other limitations. Question: Does the person have difficulty reading or writing, difficulty speaking or finding the right word, problems with balance or coordination, visual problems, numbness (face, arms, legs, hands, feet), loss of movement (face, arms, legs, hands, feet), difficulty with swallowing, or other symptom resulting from stroke?
0=No symptoms at all.	0=No symptoms at all; no limitations and no symptoms.

Appendix C: Exception from Informed Consent

Because of the emergency nature of this trial, we were unable to obtain informed consent from the participants. We chose to apply for emergency exception from informed consent (EFIC) as allowed by the FDA Docket Number FDA-2006-D-0464 and Yale IRB policy 200 PR.2.[1] Prior to beginning the study, we plan to hold community meetings in the geographic area served by each participating hospital. Individuals have the right to opt out of the study by wearing a medical alert bracelet which will be distributed at each meeting at no cost to participants. Each required component of the EFIC allowance is described below. These requirements are in addition to institutional IRB criteria. All quotes below are taken directly from the FDA policy listed above.[1]

Table 9: Exception from Informed Consent

FDA Requirement	Plan
"The human subjects are in a life-threatening situation, available treatments are unproven or unsatisfactory, and the collection of valid scientific evidence, which may include evidence obtained through randomized placebo-controlled investigations, is necessary to determine the safety and effectiveness of particular interventions."	As described in chapters 1-3, status epilepticus is time-sensitive and has significant morbidity and mortality.[2],[3]. The current guideline-recommended treatment strategy is inadequate, and the study drug may improve outcomes and decrease time to seizure cessation.
"Obtaining informed consent is not feasible because: (i) the subjects will not be able to give their informed consent as a result of their medical condition; (ii) the intervention under investigation must be administered before consent from the subjects' legally authorized representatives is feasible; and (iii) there is no reasonable way to identify prospectively the individuals likely to become eligible for participation in the clinical investigation."	Individuals in SE have a decreased level of consciousness and cannot consent. Timely intervention is imperative to improve outcomes.[4] Therefore, contacting legal representatives is not feasible and would delay care. Many individuals who present in SE are new-onset and could not be identified prior to the study. [5,6]
"Participation in the research holds out the prospect of direct benefit to the subjects because: (i) subjects are facing a life-threatening situation that necessitates intervention; (ii) appropriate animal and other preclinical studies have been conducted, and the information derived from those studies and related evidence support the potential for the intervention to provide a direct benefit to the individual subjects; and (iii) risks associated with the investigation are reasonable in relation to what is known about the medical condition of the potential class of subjects, the risks and benefits of standard therapy, if any, and what is known about the risks and benefits of the proposed intervention or activity."	Preclinical studies show benefit from ketamine administration early in SE, especially when given in conjunction with benzodiazepines. [7-9] Case reports and retrospective studies also exist that support the use of ketamine in these populations, discussed in detail in chapter 2. Risks and benefits of the study drug, as well as the standard of care are also discussed in chapter 2.
"The clinical investigation could not practicably be carried out without the waiver."	Because of the time constraints and decreased level of consciousness of potential participants, exception from informed consent is necessary to conduct prospective research.
"The proposed investigational plan defines the length of the potential therapeutic window based on scientific evidence, and the investigator has committed to attempting to contact a legally authorized representative for each subject within that window of time and, if feasible, to asking the legally authorized representative contacted for consent within that window rather than proceeding without consent. The investigator will summarize efforts made to contact legally authorized representatives and make this information available to the IRB at the time of continuing review."	SE has a narrow therapeutic window, subjects are unable to consent due to decreased level of consciousness, and it not feasible to attempt to contact the legally authorized representative (LAR) before initiating treatment.
"The IRB has reviewed and approved consent procedures and an informed consent document consistent with Sec. 50.25. These procedures and the informed consent document are to be used with subjects or their legally authorized representatives in situations where use of such procedures and documents is feasible. The IRB has reviewed and approved	Subjects, family, or LAR will be notified as early as possible without delaying care. Study team should notify either the subject or LAR/family about rights/responsibilities, risks and benefits, and prognosis. The team will answer any further questions. A written copy of this information will also be provided, with a second copy placed in study records.

procedures and information to be used when providing an opportunity for a family member to object to a subject's participation in the clinical investigation consistent with paragraph (a)(7)(v) of this section."	Study personnel will document decision to continue or withdraw.
"Additional protections of the rights and welfare of subjects will be provided, including, at least: (i) consultation (including, where appropriate, consultation carried out by the IRB) with representatives of the communities in which the clinical investigation will be conducted and from which the subjects will be drawn."	Options include community meetings, town hall meetings, focus groups, in-person surveys, random-digit dialing surveys. Each clinical site should report results of community consultation the same way and each separate community should be involved in the process.
"Additional protections of the rights and welfare of subjects will be provided, including, at least: …(ii) public disclosure to the communities in which the clinical investigation will be conducted and from which the subjects will be drawn, prior to initiation of the clinical investigation, of plans for the investigation and its risks and expected benefits; (iii) public disclosure of sufficient information following completion of the clinical investigation to apprise the community and researchers of the study, including the demographic characteristics of the research population, and its results."	The trial will be announced across the state of Connecticut, beginning before the trial begins enrollment and continuing throughout the study period. Additionally, study results will be publicized after completion.
"Additional protections of the rights and welfare of subjects will be provided, including, at least: …(iv) Establishment of an independent data monitoring committee to exercise oversight of the clinical investigation."	Coordinated by the IRB
"Additional protections of the rights and welfare of the subjects will be provided, including, at least: …(v) if obtaining informed consent is not feasible and a legally authorized representative is not reasonably available, the investigator has committed, if feasible, to attempting to contact within the therapeutic window the subject's family member who is not a legally authorized representative, and asking whether he or she objects to the subject's participation in the clinical investigation. The investigator will summarize efforts made to contact family members and make this information available to the IRB at the time of continuing review."	Medical alert bracelets declining participation in the trial are available to anyone in the community without cost. Attempts to reach legal representatives or other family must be documented uniformly and reported to the IRB
"Like other IRB records, records of the determinations above must be kept for a minimum of three years after the completion of the clinical investigation. Again, like other IRB records, these are subject to inspection and copying by FDA."	The IRB will keep trial records for at least three years in secure university storage.
"Protocols involving an exception to the informed consent requirement under this section must be performed under a separate investigational new drug application (IND) or investigational device exemption	This trial will require a new IND which must be approved by the FDA prior to enrollment. In addition, IRB approval must be obtained like any other human subjects research proposal.

(IDE) that clearly identifies such protocols as protocols that may include subjects who are unable to consent. The submission of those protocols in a separate IND/IDE is required even if an IND for the same drug product or an IDE for the same device already exists. Applications for investigations under this section may not be submitted as amendments under Secs. 312.30 or 812.35 of this chapter."	

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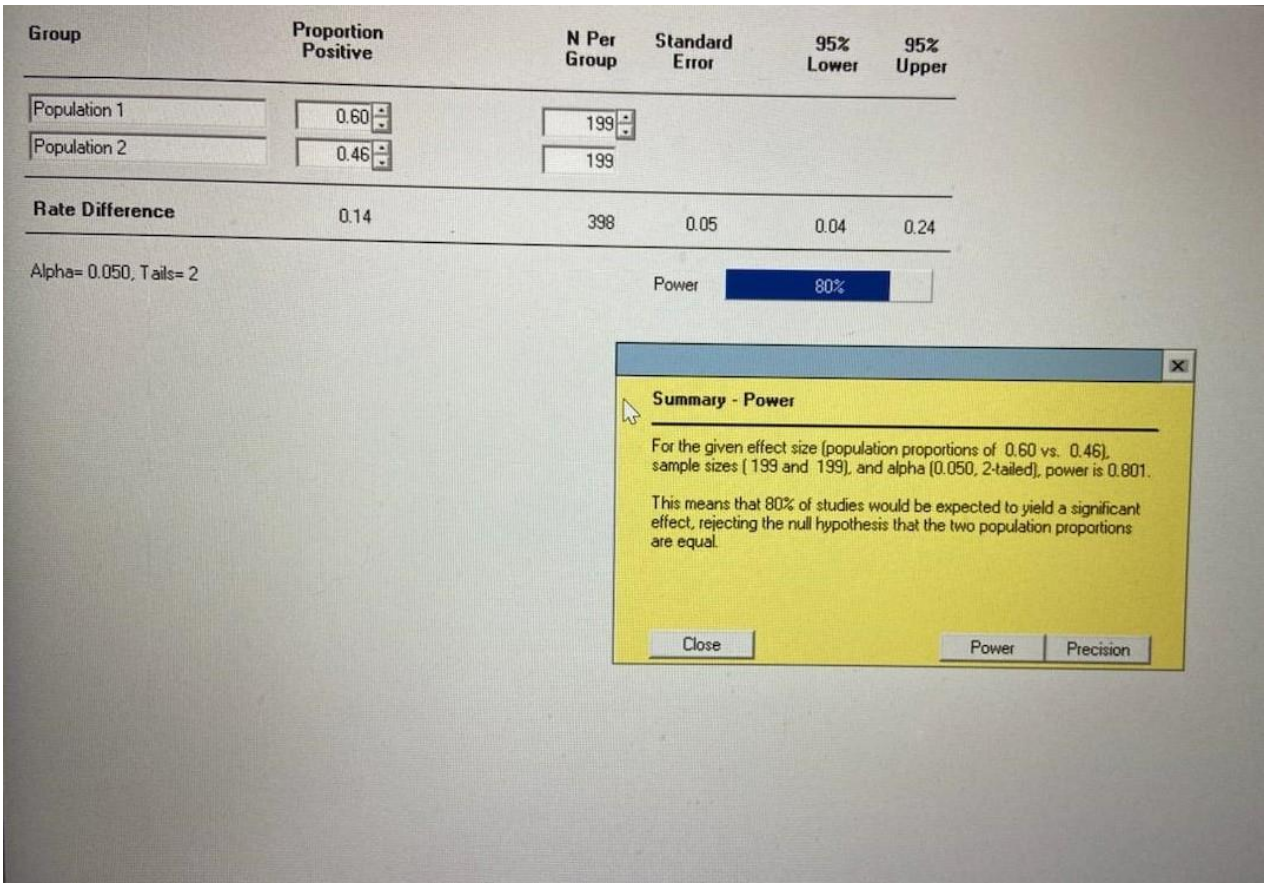
Appendix D: Sample Size Calculation

The sample size was calculated with Power and Precision software, as detailed in Chapters 2 and 3. The calculation and results are shown in the figure below.



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