Use of continuous ketamine infusion as an adjunctive agent in neonates and infants with refractory and super refractory status epilepticus

Mackenzie N. DeVine (mackenzie.devine@childrenscolorado.org)
Children's Hospital Colorado

Sharon E. Gordon
Children's Hospital Colorado

Craig A. Press
University of Colorado Anschutz Medical Campus

Research Article

Keywords: neonate, infant, refractory status epilepticus, super refractory status epilepticus, ketamine

Posted Date: May 14th, 2021

DOI: https://doi.org/10.21203/rs.3.rs-493872/v1

Abstract

Background

Continuous ketamine infusions have been studied as an adjunctive agent for refractory status epilepticus (RSE) and super refractory status epilepticus (SRSE) in older children and adults. However, minimal information exists on the efficacy, safety, and dosing for continuous ketamine in neonates and young infants. The purpose of our study was to review the safety and efficacy of continuous ketamine infusions in neonates and infants with RSE and super refractory status epilepticus (SRSE) at our institution.

Methods

Safety and clinical outcomes for neonates and infants who received continuous ketamine for RSE or SRSE at Children's Hospital Colorado between June 2019 and June 2020 were retrospectively reviewed. Patients were included if they were less than or equal to 3 months of age and received continuous ketamine infusion for RSE defined as unresolved seizures despite administration of at least one first- and at least one second-line rescue medication or SRSE defined as unresolved seizures despite administration of third-line agents.

Results

We identified three patients who met inclusion criteria and received continuous ketamine infusion for RSE or SRSE during our study period. Patients included were refractory to an average of six anti-seizure medications prior to initiation of continuous ketamine infusion. Each patient was initiated on a continuous ketamine infusion rate of 1 mg/kg/hr with one patient requiring titration to a maximum of 6 mg/kg/hr. In one case, the concomitant use of continuous ketamine allowed for a reduction in benzodiazepine continuous infusion rate. In all cases, ketamine was well tolerated especially in the setting of hemodynamic instability.

Conclusion

Ketamine may provide a safe alternative in the acute setting in severe RSE and SRSE, especially in the setting of hemodynamic instability. This is the first small retrospective study to document the use of continuous ketamine as a treatment modality in neonates and infants with RSE or SRSE secondary to various underlying etiologies without adverse events.

Background

Status epilepticus is a life-threatening neurological emergency defined as seizures lasting longer than 5 minutes or two or more sequential seizures without recovery between episodes.(1, 2) Standard therapy

includes a benzodiazepine followed by a bolus of fosphenytoin, levetiracetam, phenobarbital, and/or valproate sodium.(3) Refractory status epilepticus (RSE) refers to status epilepticus that remains unresolved despite the administration of first- and second-line anti-seizure medications and super refractory status epilepticus (SRSE) refers to seizures unresolved despite third-line agents.(4, 5) Therapy with continuous infusions of benzodiazepines, barbiturates, propofol, or ketamine can be utilized in the setting of RSE or SRSE in pediatric patients.(6) Ketamine is a general anesthetic that acts as a N-methyl-D-aspartate (NMDA) receptor antagonist to subsequently block glutamate.(7) Subanesthetic doses produce analgesia and higher doses may reduce polysynaptic spinal reflexes. While ketamine has been documented in the literature for RSE and SRSE in children, there are only two case reports of ketamine use in an infant.(8, 9) The purpose of our study was to review the safety and efficacy of continuous ketamine infusions in neonates and infants with RSE or SRSE at our institution.

Methods:

A single-center, retrospective chart review was performed at Children's Hospital Colorado. Patients who received continuous ketamine infusion between June 2019 and June 2020 were included if they were less than or equal to 3 months of age and received continuous ketamine infusion for RSE defined as unresolved seizures despite administration of at least one first- and at least one second-line seizure rescue medication or SRSE defined as unresolved seizures despite administration of third-line agents. Patients were excluded if they were greater than 3 months of age or were receiving continuous ketamine for another indication such as pain or sedation.

Three unblinded reviewers extracted retrospective data from the electronic medical record including patient demographics such as age at admission, weight, and underlying etiology of seizures. Additional clinical endpoints were collected including anti-seizure medications used prior to initiation of continuous ketamine, continuous ketamine dosing and titration, duration of continuous ketamine, concomitant anti-seizure medications during continuous ketamine, adverse effects, and clinical outcome after discontinuation of continuous ketamine. This study was approved by the Colorado Multiple Institutional Review Board and all methods were performed in accordance with the relevant guidelines and regulations of this instution. All collected information was stored on a password protected computer.

Results:

We identified three patients who received continuous ketamine infusion for RSE or SRSE during our study period. The average age at admission was 47 days and two patients (67%) were female. The underlying etiology of refractory seizures included abusive head trauma, ischemic stroke, and ischemic injury status post cardiac arrest. Patients included were refractory to an average of six anti-seizure medications prior to initiation of continuous ketamine infusion. Each patient received several boluses ranging from 1 to 1.5 mg/kg/dose prior to initiation of a continuous ketamine infusion. Each patient was initiated on a rate of 1 mg/kg/hr with one patient requiring titration to a maximum of 6 mg/kg/hr. The average duration of infusion was 5 days. Patients were maintained on an average of 3 concomitant anti-seizure medications

during continuous ketamine infusion. In one case, the concomitant use of continuous ketamine allowed for a reduction in benzodiazepine continuous infusion rate. In all cases, ketamine was well tolerated especially in the setting of hemodynamic instability. The following review describes in detail the use of continuous ketamine infusion in three infants with RSE or SRSE identified during our study period.

Patient Case 1

A 29-day-old patient born at 36 weeks gestation with no significant past medical history presented to the emergency department with low temperature, fussiness, and vomiting. On imaging, the patient was found to have bilateral subdural hemorrhages consistent with abusive head trauma. When the clinical presentation progressed to include non-suppressible rhythmic movements concerning for seizure, the patient was given lorazepam and a single dose of phenobarbital. Several hours later, fosphenytoin was given followed by three additional doses of phenobarbital and a continuous midazolam continuous infusion was initiated with no resolution of seizures. Continuous electroencephalography (EEG) was initiated on hospital day 1 that demonstrated evidence of focal seizures. Over the next three days, seizures persisted that were refractory to levetiracetam, continuous midazolam, two pentobarbital-induced burst suppressions, and maintenance therapy with phenobarbital and levetiracetam, as outlined in the Table.

Due to failure of multiple therapies and subsequent hemodynamic instability requiring vasoactive support with epinephrine, a continuous ketamine infusion was initiated on hospital day 7. Following two ketamine boluses (2 mg/kg IV), an infusion was initiated at 1 mg/kg/hr and titrated to a maximum rate of 4.5 mg/kg/hr over two days (Figure). Lacosamide was started as an additional adjunctive agent. Following 5 days of ketamine infusion without successful capture of subclinical seizures, the decision was made to stop continuous EEG and monitor for clinical seizures. Ketamine was weaned off over the next 24 hours. The patient was maintained on lacosamide, levetiracetam, topiramate, and phenobarbital and an EEG on day 14 of hospitalization showed resolution of seizures (Table). The patient experienced significant hypoglycemia throughout the clinical course requiring infusion with dextrose 25%. The hypoglycemia was initially thought to be secondary to acute illness and ketamine, however, further workup attributed it to adrenal insufficiency secondary to traumatic brain injury. No other significant adverse events were reported.

Patient Case 2

A 52-day-old patient born at 33 weeks with a vein of Galen malformation developed status epilepticus. The patient's course prior to seizure onset included vein of Galen embolization and a subsequent postoperative complication of ischemic stroke. At approximately day of life 50, the patient began to demonstrate frequent, repetitive hemiclonic seizures and a decline in clinical stability. Further imaging showed new areas of ischemia, consistent with a new stroke. Several doses of lorazepam, phenobarbital, fosphenytoin, and levetiracetam were given before the patient was started on a midazolam continuous infusion that was quickly titrated to 0.5 mg/kg/hr for both hemiclonic and subclinical seizures (Table). To optimize cerebral blood flow and control refractory seizures, a ketamine 1 mg/kg IV bolus was given,

followed by initiation of a ketamine continuous infusion at 1 mg/kg/hr (Figure). Seizures ceased within one hour of initiation of ketamine in conjunction with midazolam. The midazolam infusion rate was slowly decreased from 0.5 mg/kg/hr to 0.1 mg/kg/hr within 60 hours of initiation of continuous ketamine.

The patient continued midazolam and ketamine continuous infusions until 36 hours without evidence of seizures. During this time, the patient experienced periods of hypotension thought to be secondary to midazolam. Thus, midazolam infusion was weaned prior to ketamine and hypotension improved. Levetiracetam maintenance therapy was initiated after discontinuation of midazolam and ketamine continuous infusions. The following day, the patient demonstrated signs of clinical seizures and ketamine continuous infusion was reinitiated at 1 mg/kg/hr. The infusion was titrated to a rate of 1.5 mg/kg/hr before resolution of seizures and subsequent discontinuation the following day. Intracranial pressure measurements were 5 to 12 millimeters of mercury throughout the infusion measured via external ventricular drain. Levetiracetam maintenance therapy was increased, and additional seizures were managed with topiramate and ketamine boluses (Table). The patient was discharged on hospital day 75.

Four days later, the patient was readmitted after parents noted right sided leg shaking, left eye deviation, and lip smacking that was unresolved despite a dose of levetiracetam at home. The patient was brought into the emergency department and received two doses of intranasal midazolam followed by fosphenytoin for persistent lip smacking. The patient was subsequently transferred to the neonatal intensive care unit (NICU) for intubation and management of refractory seizures. The patient received additional IV midazolam, oral topiramate, and IV phenobarbital upon arrival to the NICU for persistent clinical seizures. On hospital day 2, continuous EEG was placed, and the patient received an additional dose of IV phenobarbital and 1 mg/kg of IV ketamine followed by a continuous ketamine infusion at 1 mg/kg/hr with resolution of clinical seizures, but persistent subclinical seizures on continuous EEG. On hospital day 3, the continuous ketamine was titrated to 3 mg/kg/hr without resolution of subclinical seizures and a midazolam 0.1 mg/kg IV bolus was given followed by a continuous infusion at 0.1 mg/kg/hr. On hospital day 4, lacosamide was given until initiation of clobazam maintenance on hospital day 10.

The patient was maintained on continuous ketamine (maximum rate 6 mg/kg/hr on hospital day 8) and midazolam (maximum rate 0.9 mg/kg/hr on hospital day 9) through hospital day 14. Complete dose titration details of continuous ketamine can be found in the Figure. The patient continued to receive intermittent boluses of midazolam, ketamine, phenobarbital, and fosphenytoin for subclinical seizures. Phenobarbital was added on hospital day 14 as well. Subclinical seizure activity significantly decreased on hospital day 14 and continuous EEG was discontinued. The patient was extubated on hospital day 18 and repeat magnetic resonance imaging demonstrated no new cerebral infarct. Repeat EEG on hospital day 25 showed no evidence of seizures and the patient was discharged home on phenobarbital, topiramate, and clobazam maintenance therapy. Each continuous ketamine infusion was well-tolerated with no additional adverse effects noted.

Patient Case 3

A 60-day-old patient born at term with no past medical history presented to the emergency department with respiratory distress and was found to have severe cardiomegaly on chest x-ray. Further diagnostics revealed anomalous left coronary artery from the pulmonary artery which required surgical intervention on day 2 of hospitalization. On day 4 of hospitalization, the patient became hypotensive and bradycardic, requiring chest compressions and cannulation to veno-arterial extracorporeal membrane oxygenation. Neuroprotective measures including therapeutic hypothermia and targeted normotension were implemented post-arrest and imaging was reassuring against significant multiorgan damage, including a normal head ultrasound.

Multifocal seizures were identified on via continuous EEG on day 5 of hospitalization and were initially treated with IV lorazepam, levetiracetam and fosphenytoin. Maintenance levetiracetam was then initiated. The patient's seizures continued and were refractory to additional doses of fosphenytoin and phenobarbital until initiation of midazolam and pentobarbital continuous infusions. On day 7 of hospitalization, the patient developed severe lactic acidosis and worsening kidney function thought to be secondary to propylene glycol toxicity from pentobarbital (Table). The patient was transitioned to continuous renal replacement therapy (CRRT) and pentobarbital was discontinued. Due to continued seizures and initiation of CRRT, the decision was made to initiate a continuous ketamine infusion. A bolus dose of ketamine 1 mg/kg IV was given followed by a continuous infusion at 1 mg/kg/hr (Figure). The infusion was titrated to 2 mg/kg/hr over the next 24 hours. No adverse effects were noted throughout the course of the infusion. The family chose to limit life sustaining therapy on day 8 and the patient died shortly thereafter.

Discussion

Continuous ketamine was used as an adjunctive treatment modality in three neonates/infants with RSE or SRSE at our institution during the study period. In one case, the concomitant use of continuous ketamine allowed for a reduction in benzodiazepine dosing. In all cases ketamine was added after aggressive therapy for refractory or super refractory status epilepticus. In 2/3 cases, seizures resolved with therapy including ketamine, with one patient having a temporally associated dramatic improvement in seizures after initiating ketamine.

A recent retrospective review reported that ketamine use has significantly increased for severe pediatric status epilepticus, especially after pentobarbital.(7) Ketamine may play an important role in patients who demonstrate poor response to other anti-seizure medications, however, its safety and efficacy in neonates and young infants is unclear. Additionally, as with many anti-seizure medications, the true risk of administering ketamine in neonates and infants and the impact on the developing brain is not known. (10)

The pathogenesis of RSE/SRSE makes ketamine an attractive option for management. During RSE/SRSE, NMDA receptors also increase, leading to prolonged neuronal hyperexcitability.(8) Ketamine, as a noncompetitive NMDA receptor antagonist, decreases this excitotoxicity.(11) Ketamine has positive effects on hemodynamic properties such as heart rate and blood pressure, which could mitigate the cardiovascular compromise observed when higher doses are given of other anticonvulsants, namely benzodiazepines.(13) Additionally, RSE is known to decrease activated gamma-aminobutyric acid (GABA) receptors and increase inactivated GABA receptors. These physiologic changes render many GABA modulators, namely benzodiazepines, less effective with time.(14) The decreased responsiveness to agents targeting synaptic GABA receptors may be overcome by higher doses, but with an increase in adverse effects such as respiratory and cardiovascular compromise.(7) Ketamine may increase the recycling and expression of synaptic GABA receptors during RSE, however, this proposed mechanism remains controversial.(15) Additional prospective studies are warranted to determine the safety and efficacy of continuous ketamine for RSE and SRSE in infants and neonates.

Conclusions

This is the first retrospective study, to our knowledge, to document the use of continuous ketamine in the acute setting as a treatment modality in neonates and infants with RSE and SRSE secondary to various underlying etiologies. Continuous ketamine infusion may be considered in neonates and young infants with refractory status epilepticus after failure of other first- and second-line therapies, with special attention where hemodynamic instability is preventing escalation of other therapies. Further studies are needed to evaluate the long-term safety and efficacy of continuous ketamine in this patient population.

Declarations

Ethics Approval and Consent to Participate: This study was approved by the Colorado Multiple Institutional Review Board and consent to participate in this study was waived.
Consent for Publication: Not applicable.
Availability of Data and Material: The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.
Competing Interests: The authors declare that they have no competing interests.
Funding: This study was not funded.
Authors' Contributions: MD and SG designed data collection tools, collected and analyzed data, wrote the main manuscript, and prepared all figures. CP analyzed data, wrote the main manuscript, and revised all figures. All authors reviewed the manuscript.
Acknowledgements: Not applicable.

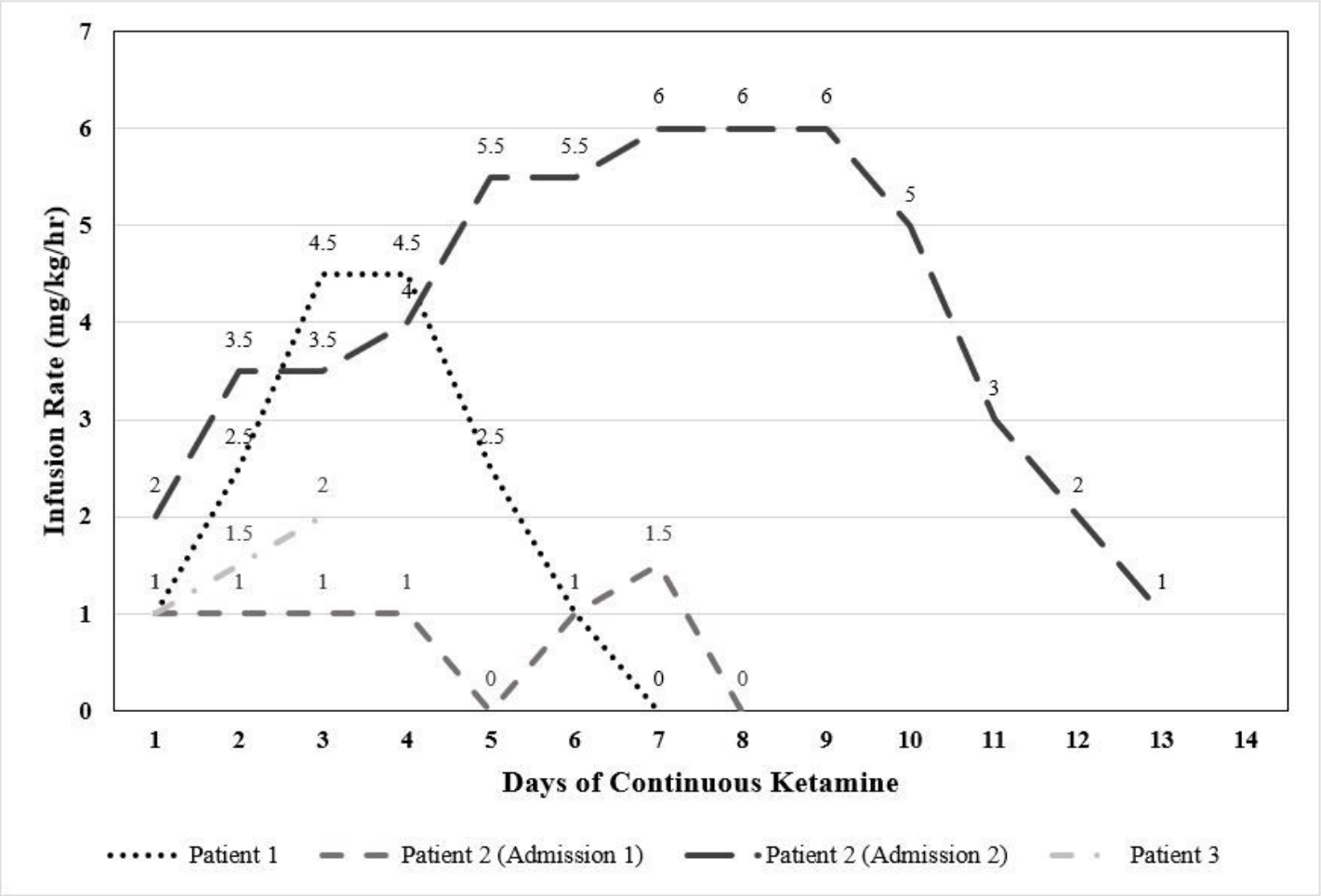
References

1. Glauser T, Shinnar S, Gloss D, Alldredge B, Arya R, Bainbridge J, et al. Evidence-Based Guideline: Treatment of Convulsive Status Epilepticus in Children and Adults: Report of the Guideline

Committee of the American Epilepsy Society. Epilepsy Curr. 2016;16(1):48-61.

2. Trinka E, Cock H, Hesdorffer D, Rossetti AO, Scheffer IE, Shinnar S, et al. A definition and classification of status epilepticus–Report of the ILAE Task Force on Classification of Status Epilepticus. Epilepsia. 2015;56(10):1515-23.
3. Kapur J, Elm J, Chamberlain JM, Barsan W, Cloyd J, Lowenstein D, et al. Randomized Trial of Three Anticonvulsant Medications for Status Epilepticus. N Engl J Med. 2019;381(22):2103-13.
4. Abend NS, Dlugos DJ. Treatment of refractory status epilepticus: literature review and a proposed protocol. Pediatr Neurol. 2008;38(6):377-90.
5. Vasquez A, Farias-Moeller R, Tatum W. Pediatric refractory and super-refractory status epilepticus. Seizure. 2019;68:62-71.
6. Claassen J, Hirsch LJ, Emerson RG, Mayer SA. Treatment of refractory status epilepticus with pentobarbital, propofol, or midazolam: a systematic review. Epilepsia. 2002;43(2):146-53.
7. Keros S, Buraniqi E, Alex B, Antonetty A, Fialho H, Hafeez B, et al. Increasing Ketamine Use for Refractory Status Epilepticus in US Pediatric Hospitals. J Child Neurol. 2017;32(7):638-46.
8. Tarocco A, Ballardini E, Garani G. Use of ketamine in a newborn with refractory status epilepticus: a case report. Pediatr Neurol. 2014;51(1):154-6.
9. Huntsman RJ, Strueby L, Bingham W. Are Ketamine Infusions a Viable Therapeutic Option for Refractory Neonatal Seizures? Pediatr Neurol. 2020;103:8-11.
10. Andropoulos DB. Effect of Anesthesia on the Developing Brain: Infant and Fetus. Fetal Diagn Ther. 2018;43(1):1-11.
11. Yuan C, Zhang Y, Zhang Y, Cao S, Wang Y, Fu B, et al. Effects of Ketamine on Neuronal Spontaneous Excitatory Postsynaptic Currents and Miniature Excitatory Postsynaptic Currents in the Somatosensory Cortex of Rats. Iran J Med Sci. 2016;41(4):275-82.
12. Andropoulos DB, Greene MF. Anesthesia and Developing Brains - Implications of the FDA Warning. N Engl J Med. 2017;376(10):905-7.
13. Golub D, Yanai A, Darzi K, Papadopoulos J, Kaufman B. Potential consequences of high-dose infusion of ketamine for refractory status epilepticus: case reports and systematic literature review. Anaesth Intensive Care. 2018;46(5):516-28.
14. Deeb TZ, Maguire J, Moss SJ. Possible alterations in GABAA receptor signaling that underlie benzodiazepine-resistant seizures. Epilepsia. 2012;53 Suppl 9:79-88.
15. Wang DS, Penna A, Orser BA. Ketamine Increases the Function of gamma-Aminobutyric Acid Type A Receptors in Hippocampal and Cortical Neurons. Anesthesiology. 2017;126(4):666-77.

Figures



*Rate immediately prior to withdrawal of care
**Patient 3 required extracorporeal membrane oxygenation support during ketamine course

Figure 1

Continuous ketamine titration

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- DeVineetalKetamineBMCNeurologyTable.docx