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INVITED COMMENTARY

Ketamine for Status Epilepticus in Children: Searching for the Right Drug for the Right Patient

Kristin P. Guilliams[1*] and Dana Harrar[2]

Pediatric convulsive status epilepticus has a yearly incidence of ~ 20/100,000 in the United States and Europe [1], and many children develop refractory status epilepticus, defined as failure to respond to two appropriately dosed parenteral antiseizure medications, including a benzodiazepine [2]. Mortality rates are approximately 5% for children requiring intensive care unit admission [3], and survivors have risks of cognitive and other neurologic sequelae.

Unfortunately, effective treatments for refractory status epilepticus continue to elude us. Once loading doses of benzodiazepines and other antiseizure medications have failed to control seizures, providers often reach for continuous infusions of anesthetic drugs that act on gamma-aminobutyric acid (GABA) receptors. Midazolam has historically been used first, followed by pentobarbital if seizures persist [4]. Unfortunately, these agents control seizures in only a subset of patients, and their administration is often accompanied by side effects, including hypotension [4]. The partial efficacy of GABA-ergic agents may reflect the molecular mechanisms at play during status epilepticus. As seizures persist, GABA receptors are internalized, while N-methyl-D-aspartate (NMDA) receptors are trafficked to the synapse, creating a vicious cycle perpetuating excitation. This suggests that an agent targeting excitatory mechanisms may prove especially useful, either on its own or in conjunction with GABA-acting agents.

In this issue, Jacobwitz et al. [5] report their experience using ketamine, an NMDA receptor antagonist, as a first-line anesthetic infusion in pediatric patients with status epilepticus. In "A Comparison of Ketamine Versus Midazolam as First-Line Anesthetic Infusions for Pediatric Status Epilepticus," the authors describe 117 children with refractory status epilepticus cared for at a large children's hospital over a 5-year period, 79 (68%) of whom received midazolam as the first-line anesthetic infusion and 38 (32%) of whom received ketamine. The decision to use midazolam versus ketamine as the first-line infusion was at the discretion of the treating team and was not formalized as part of an institutional protocol. The authors observed that seizures were more likely to terminate with ketamine than midazolam, and adverse effects occurring during or within 12 h of the last anesthetic administration were more frequently observed with midazolam than ketamine.

Ketamine was first approved for clinical use as a short-acting general anesthetic agent by the Food and Drug Administration in 1970. There was initial enthusiasm for its antiexcitatory and potential neuroprotective effects, but this was dampened by reports associating ketamine with increased intracranial pressure in children [6]. Skepticism regarding ketamine was compounded by neuropathologic studies demonstrating neuronal vacuolization and mitochondrial depletion in rats exposed to high doses [7], and ketamine use became relatively infrequent in pediatric patients after both rodent and nonhuman primate models reported developmental sensitivity to NMDA receptor blockade, with ketamine triggering apoptosis and neuronal degeneration in young brains

*Correspondence: kristinguilliams@wustl.edu
[1] Departments of Neurology, Pediatrics, and Radiology, Washington University School of Medicine, 660 S. Euclid Ave MSC 8111-43-1260, St. Louis, MO 63110, USA
Full list of author information is available at the end of the article

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after only brief exposure [8]. However, ketamine's affinity for thalamocortical pathways allows for dissociative anesthetic effects at doses that do not simultaneously impact brainstem respiratory centers. This, along with its systemic release of endogenous catecholamine stores, make ketamine an attractive anesthetic agent for patients with cardiopulmonary instability. Additional reports showing variable changes or consistently decreased [9] intracranial pressure in mechanically ventilated children with controlled carbon dioxide levels have mitigated concerns about ketamine causing increased intracranial pressure. In combination with the unique and appealing side effect profile, this has led to steadily increasing use of ketamine in pediatric intensive care units in recent years, including in children with neurocritical illness [10] and status epilepticus [11]. However, studies to date have described the use of ketamine as a second-line or third-line anesthetic infusion for status epilepticus, and data regarding earlier use are sparse. Ketamine as a first-line anesthetic is intriguing to consider as animal studies suggest earlier administration may increase the possibility of neuroprotective effects of ketamine in status epilepticus [12]. Less total drug exposure may be a clue to reconciling the seemingly conflicting observations of neuroprotection versus neurotoxicity of ketamine [13] and warrants further study.

Although the study by Jacobwitz et al. [5] supports early NMDA antagonism for the treatment of status epilepticus, it is noteworthy that children in the study who died were more likely to have received ketamine as a first-line agent than midazolam, despite midazolam being used twice as frequently. This retrospective study is limited in its ability to fully understand this observation, but this certainly warrants careful thought and consideration. There are at least three possibilities for this finding, which future studies will help clarify. First, it is possible that these children's fragility prompted the clinicians to reach first for ketamine, and the children were so sick that even stopping their seizures could not reverse their overall clinical course. In support of this, the treatment groups were unbalanced in their baseline characteristics: Children treated with ketamine were younger and more likely to have cardiac disease and acute symptomatic seizures, whereas those treated with midazolam were more likely to have preexisting epilepsy. Future studies with balanced cohorts will help clarify this. Second, this may simply be a statistical type 1 error, and larger, multicenter cohorts will reveal whether this association persists. Finally, it is possible that ketamine played an unknown contributory role in the untoward outcome. Although the authors were careful to look for immediate adverse effects in both groups, there may be additional downstream cascades that remain to be elucidated or to which only certain populations of children may be vulnerable. A recent study of the effects of ketamine in the setting of influenza found delayed severe weight loss and death when animals were exposed to both ketamine and influenza simultaneously, but neither occurred with individual exposure [14]. This study highlights there are still many unknown effects of ketamine, including, but not limited to, its systemic immunomodulatory effects [15]. Future studies should be vigilant in looking for possible off-target effects that may influence clinician's overall risk–benefit assessments when choosing the best drug for their patient.

Refractory status epilepticus is a challenging and potentially devastating disease. Both prolonged anesthesia and prolonged seizures carry risks, particularly in the developing brain. Ketamine's unique mechanism offers promise that this may be a tool in the arsenal against status epilepticus, but more studies are needed to understand how to best wield it for good.

Author details
[1] Departments of Neurology, Pediatrics, and Radiology, Washington University School of Medicine, 660 S. Euclid Ave MSC 8111-43-1260, St. Louis, MO 63110, USA. [2] Division of Child Neurology, Children's National Hospital, 111 Michigan Ave, NW, Washington, District of Columbia 20010, USA.

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References

1. Chin RFM, Neville BGR, Peckham C, et al. Incidence, cause, and short-term outcome of convulsive status epilepticus in childhood: prospective population-based study. Lancet. 2006;368(9531):222–9. https://doi.org/10.1016/S0140-6736(06)69043-0.
2. Hirsch LJ, Gaspard N, van Baalen A, et al. Proposed consensus definitions for new-onset refractory status epilepticus (NORSE), febrile infection-related epilepsy syndrome (FIRES), and related conditions. Epilepsia. 2018;59(4):739–44. https://doi.org/10.1111/epi.14016.
3. Lacroix J, Deal C, Gauthier M, Rousseau E, Farrell CA. Admissions to a pediatric intensive care unit for status epilepticus: a 10-year experience. Crit Care Med. 1994;22(5):827–32. https://doi.org/10.1097/00003246-199405000-00019.
4. Tasker RC, Goodkin HP, Sánchez Fernández I, et al. Refractory status epilepticus in children: intention to treat with continuous infusions of midazolam and pentobarbital. Pediatr Crit Care Med. 2016;17(10):968–75. https://doi.org/10.1097/PCC.0000000000000900.
5. Jacobwitz M, Mulvihill C, Kaufman MC, et al. A comparison of ketamine versus midazolam as first-line anesthetic infusions for pediatric status epilepticus. Neurocrit Care. 2023. https://doi.org/10.1007/s12028-023-01859-2.

6. Evans J, Rosen M, Weeks RD, Wise C. Ketamine in neurosurgical procedures. Lancet. 1971;297(7688):40–1. https://doi.org/10.1016/S0140-6736(71)80041-7.
7. Olney JW, Labruyere J, Price MT. Pathological changes induced in cerebrocortical neurons by phencyclidine and related drugs. Science. 1989;244(4910):1360–2.
8. Ikonomidou C, Bosch F, Miksa M, et al. Blockade of NMDA receptors and apoptotic neurodegeneration in the developing brain. Science. 1999;283(5398):70–4. https://doi.org/10.1126/science.283.5398.70.
9. Mayberg TS, Lam AM, Matta BF, Domino KB, Winn HR. Ketamine does not increase cerebral blood flow velocity or intracranial pressure during isoflurane/nitrous oxide anesthesia in patients undergoing craniotomy. Anesth Analg. 1995;81(1):84–9. https://doi.org/10.1097/00000539-199507000-00017.
10. Loi MV, Lee JH, Huh JW, et al. Ketamine use in the intubation of critically ill children with neurological indications: a multicenter retrospective analysis. Neurocrit Care. 2023. https://doi.org/10.1007/s12028-023-01734-0.
11. Keros S, Buraniqi E, Alex B, et al. Increasing ketamine use for refractory status epilepticus in US pediatric hospitals. J Child Neurol. 2017;32(7):638–46. https://doi.org/10.1177/0883073817698629.
12. Stewart LS, Persinger MA. Ketamine prevents learning impairment when administered immediately after status epilepticus onset. Epilepsy Behav EB. 2001;2(6):585–91. https://doi.org/10.1006/ebeh.2001.0272.
13. Wu GH, Guo QH, Xu XD, et al. Ketamine exerts dual effects on the apoptosis of primary cultured hippocampal neurons from fetal rats in vitro. Metab Brain Dis. 2023. https://doi.org/10.1007/s11011-023-01236-0.
14. Nash PB, Hemphill MA, Barron JN. Administration of ketamine/xylazine increases severity of influenza (A/Puerto Rico/8/34) in mice. Heliyon. 2023;9(3):e14368. https://doi.org/10.1016/j.heliyon.2023.e14368.
15. Ali HM, Mokhtar AM. Effect of single compared to repeated doses of intravenous S(+) ketamine on the release of pro-inflammatory cytokines in patients undergoing radical prostatectomy. Anesth Essays Res. 2017;11(2):282–6. https://doi.org/10.4103/aer.AER_28_17.