JPPT | Letter to the Editor

Assessing the Effect of Ketamine on Suprarefractory Status Epilepticus Requires Appropriately Designed Cohort Studies

To the Editor.—I read with interest the article by DeVine et al[1] on 3 pediatric patients with suprarefractory status epileptics (SRSE): patient 1, age 29 days, with traumatic brain injury; patient 2, age 52 days, with ischemic stroke due to venous malformation; and patient 3, age 60 days, with hypoxic brain injury, who benefited from ketamine continuously administered during 5 days in addition to a number of other antiseizure drugs. It was concluded that continuous ketamine infusion should be considered in SRSE.[1] The study is compelling but has limitations that should be discussed.

The main limitation of the study is the design. It is not possible to draw general conclusions from 3 patients. To assess the effect of a medication a multicenter, prospective, randomized, controlled trial would be desirable. It is also mandatory that the size of the verum group be large enough to allow comparison with healthy controls or a control population with the disease.

Because the effect of ketamine may strongly depend on the underlying cause of epilepsy, on comorbidities, and on the current medication, it is mandatory to know the underlying cause of epilepsy and the comorbidities of the 3 included patients. Patient 1 had severe hypoglycemia throughout hospitalization.[1] How was hypoglycemia ruled out as the driver of the SRSE? Regarding the cause of epilepsy, we should know how genetic causes of epilepsy were ruled out.

We disagree with the notion that the index study is the first in which continuous ketamine infusions have been used to treat SRSE.[1] Continuous ketamine has been previously used to treat SRSE.[3]

Not sufficiently discussed in the study are the side effects of ketamine. Although it is generally well tolerated, ketamine can exhibit severe side effects in single patients, such as delirium, headache, hallucinations, nausea, vomiting, arterial hypertension, and abdominal compartment syndrome.[2,3]

There is no mention that ketamine is not effective in each patient with status epilepticus. In a study of 69 pediatric patients with RSE, seizure termination could be achieved in only 46%, seizure reduction in 28%, and no change was observed in 26%.[3] In a study of 11 adult patients with status epilepticus, permanent status epilepticus control could be achieved in only 27% of patients.[4] In a study of 68 adult patients with SRSE, complete cessation of SRSE could be achieved in 63% of cases.[5]

Regarding the patient with ischemic stroke, we should know the initial treatment of ischemic stroke, particularly whether or not the patient underwent thrombolysis or thrombectomy and to what degree the National Institute of Health Stroke Scale score changed before and after acute therapy.

A treatment of status epilepticus, including RSE and SRSE, that has not been applied and discussed is the ketogenic diet. From ketone bodies it is known that they have an antiseizure effect and it would be interesting to know if ketamine plus ketogenic diet potentiates the antiseizure effect of ketamine. Although the ketogenic diet is usually well tolerated, it may have side effects in single patients.

Overall, the interesting study has limitations that put the results and their interpretation into perspective. Addressing these issues would strengthen the conclusions and could improve the status of the study. Assessing the effect of ketamine on SRSE requires appropriately designed cohort studies.

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AUTHOR'S RESPONSE: We thank Dr Finsterer for his comments in the Letter to the Editor in response to our article summarizing our center's experience with the use of ketamine for the treatment of refractory status epilepticus (RSE) and superrefractory status epilepticus (SRSE) in young infants. We agree that broad conclusions about the efficacy and safety of ketamine for status epilepticus will require further investigation. However, multicenter randomized studies for the treatment of status epilepticus in very young patients are unlikely to occur in the near future. Currently, there are no ongoing clinical trials evaluating the use of ketamine for RSE in children on Clinicaltrials.gov (searched August 6, 2023). The publication of case series and larger cohorts provides critical knowledge from real-world experiences treating status epilepticus in specific populations. This includes the larger cohort of patients published after this manuscript was accepted.

We agree with Dr Finsterer's point that understanding the underlying etiology is critical to interpreting response to any therapy. In the cases presented, given the rarity of the clinical scenarios we were describing, we limited details intentionally to avoid providing details that would risk identifying patients. Hypoglycemia was managed for the first patient with dextrose infusions; the time course of the seizures and presence outside of the hypoglycemia were more consistent with acute symptomatic seizures secondary to inflicted trauma. All cases had a proximate injury to provoke the episode of status epilepticus, and genetic evaluations were not necessary at the time. Regarding the specifics of the patient with ischemic stroke, this was related to a vascular malformation and not due to an acute end vessel occlusion. Use of thrombolytics or mechanical thrombectomy was not indicated. The Pediatric National Institutes of Health Stroke Scale is validated in children ages 2 to 18 years, but it is not intended for use in infants.

We did not include a thorough discussion of potential adverse reactions to ketamine in our discussion and appreciate the attention Dr Finsterer brought to this. We discussed adverse events that were noted and described the presence or absence of some common adverse reactions reported with ketamine. Further, we agree that the efficacy of ketamine for RSE and SRSE in different clinical scenarios needs further study because not all patients in our series had a complete or sustained response.

Research to understand the role of bolus and infusions of ketamine in the treatment of SE in children is essential given the expanding use of ketamine for the treatment of seizures in children.

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