

Ketamine for Status Epilepticus: Canadian Physician Views and Time to Push Forward

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Changes at the molecular level in prolonged status epilepticus (SE) lead to unwanted pharmaco-resistance patterns. Initial down-regulation of gamma amino butyric acid receptors, followed by receptor subunit changes, leads to resistance to gamma amino butyric acid-mediated medications.¹ Upregulation of p-glycoprotein transport molecules at the blood-brain barrier lead to export of phenytoin and phenobarbital molecules.¹ Finally, upregulation of N-methyl d-aspartate (NMDA) receptors occurs, leading to glutamate-mediated excitotoxicity and seizure potentiation.

Targeting NMDA receptors via an antagonist provides an avenue for treating SE that is not achieved by other antiepileptic drugs (AEDs). Ketamine is an NMDA receptor antagonist that is readily available and relatively inexpensive. However, concerns over its effects on cerebral blood flow and intracranial pressure (ICP) have been propagated throughout the emergency medicine and critical care literature since the 1960s. However, recent reviews of ketamine use in traumatic brain injury² and nontraumatic neurological illness³ fail to demonstrate such phenomena.

We suspected Canadian physicians involved in the management of SE would not commonly report ketamine usage in their patients based on the described literature and would be reluctant to prescribe without an epileptologist's opinion. Thus, we conducted a small survey of Canadian physicians that treat SE and refractory status epilepticus (RSE) to document this and assess respondents' willingness to participate in a prospective evaluation of ketamine in SE and RSE.

METHODS

Target Population

We targeted neurologists, neurosurgeons, and intensivists/neurointensivists across Canada. Our goal was to survey those physicians most likely to take care of patients with status epilepticus. E-mail contact was made with department heads requesting participation from all neurology, neurosurgery, and critical care departments across the major academic/university-affiliated teaching hospitals in Canada. The survey was also sent to the Canadian Neurological Science Federation and disseminated in a newsletter to all members. Responses were collected between September 2013 and January 2014.

Survey Design

We designed a short Survey Monkey survey of 21 questions. The first five questions focused on respondent demographics: subspecialty, years of experience, and intensive care unit (ICU) environment

for treating SE. The next two questions focused on identifying the three first-tier and three second-tier AEDs prescribed for SE. The remaining 14 questions focused on respondents' experience with ketamine in status epilepticus and asked about previous use, use in neurology/neurosurgery patients, seizure response, number of AEDs before use, future plans to use, and knowledge of the literature surrounding ketamine in SE. A list of survey questions is seen in Appendix A of the supplementary materials.

Validation

Using a roundtable Delphi method,⁴ a panel of three anonymous physicians trialed the survey, providing feedback and validation of content before survey dissemination. These three physicians were practicing critical care doctors with at least five years of current ICU practice caring for patients with status epilepticus.

RESULTS

Respondent Demographics

We received 44 responses between September 2013 and January 2014. The respondents' subspecialties were: intensivist (46.5%), neurologist (27.9%), and neurosurgeon (25.6%). Only 53.5% of physicians provided primary care to patients in the ICU, with an average of eight years of ICU experience (range: 1–35 years). Patients with SE or RSE were reported to be cared for in mixed medical/surgical ICU, surgical ICU, medical ICU, neuro-ICU, neurosurgical stepdown, and epilepsy units in 62.7%, 20.93%, 16.28%, 9.3%, 20.93%, and 13.95%, respectively. Sixty-five percent of respondents reported these units as “closed” units.

AED Choices for SE

Benzodiazepines, phenytoin, and propofol were the three commonly reported first-tier AEDs at 50%, 44.7%, and 26.3%, respectively. Similarly, the three commonly reported second-tier AEDs were midazolam, levetiracetam, and phenobarbital at 18.4%, 18.4%, and 27.3%, respectively. Phenobarbital was reported as the first-, second-, third-, fourth-, fifth-, and sixth-line

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Table 1: Respondent Choices for AEDs in SE and RSE

	1 st Line (% of Respondents)	2 nd Line (% of Respondents)	3 rd Line (% of Respondents)	4 th Line (% of Respondents)	5 th Line (% of Respondents)	6 th Line (% of Respondents)
Benzodiazepines	50.0	5.3	7.9	23.7	11.4	0
PHT	50.0	44.7	2.6	0	0	0
Levetiracetam	0	21.1	18.4	18.4	8.6	15.2
PHB	0	2.6	13.2	13.2	14.3	27.3
CBZ	0	2.6	7.9	2.6	2.9	0
Propofol	0	10.5	26.3	18.4	22.9	12.1
VPA	0	13.2	21.1	10.5	20.0	3.0
Lacosamide	0	0	2.6	0	5.7	3.0
Ketamine	0	0	0	2.6	5.7	6.1
Topiramate	0	0	0	2.6	2.9	6.1
Volatile Gas	0	0	0	0	2.9	12.1
Clobazam	0	0	0	2.6	0	6.1

AEDs = anti-epileptic drugs, SE = status epilepticus, RSE = refractory status epilepticus, PHT = phenytoin, PHB = phenobarbital, CBZ = carbamazepine, VPA = valproic acid.

AED choice in 0.5%, 2.6%, 13.2%, 13.2%, 14.3%, and 27.3%, respectively. Continuous midazolam infusions were reported as the first-, second-, third-, fourth-, fifth-, and sixth-line AED choice in 0%, 0%, 5.3%, 18.4%, 11.5%, and 0%, respectively.

Finally, ketamine was reported as fourth, fifth, and sixth choices in 2.6%, 5.7%, and 6.1% of respondents, respectively. Respondents' choices for AEDs are shown in Table 1.

Ketamine Experience

Overall, 47.4% of respondents reported using ketamine for RSE in the past. Only 23.7% reported its use in neurosurgical patients with SE or RSE, whereas 42.1% used it in the neurology patient population. The mean number of patients treated with ketamine for SE was two (range: 0–15). The mean number of AEDs on board before using ketamine was reported as four (range: 0–5).

The decision to initiate ketamine therapy was independently made by the respondent in 27.6%. Combined decision to treat via the respondent and an epileptologist occurred in 41.4%, whereas the respondent left the decision to an epileptologist in 31.0% of cases.

Seizures were reported to have ceased in all patients by 10.3% of respondents. Respondents reported majority response (>50% of patients), minority response (<50% of patients), and no response in 13.8%, 37.9%, and 37.9%, respectively. Based on these experiences, 67.9% of respondents would consider ketamine again for SE, with 48.3% considering it earlier in their treatment algorithm.

When asked about their view of ketamine in SE, 75.8% of respondents viewed it as experimental, with only 12.1% comfortable prescribing it independently in the future and only 45.2% being aware of the emerging literature on ketamine for SE and RSE. However, 74.2% of respondents indicated they would participate in a prospective study of early ketamine therapy for SE and RSE.

DISCUSSION

Aversion to the use of ketamine in the neurological population has been present in the critical care, emergency medicine, and

neuroscience communities since the late 1960s. Small retrospective case series/reports from the 1960s and 1970s displayed adverse ICP responses to ketamine when used as an anesthetic agent in shunt revisions.^{2,3} The elevated ICP seen in these small series, with unconventional anesthetic practices, has led to concerns over ketamine use in the neurological population that has propagated over the past 40 to 50 years. Recent systematic review on the ICP effect of ketamine in traumatic and nontraumatic neurological illness displayed Oxford level 2b, GRADE C, evidence against ICP concerns with ketamine. Similarly, cerebral perfusion pressure was seemingly preserved.

Given existing literature on the use of ketamine in the neurological population, we suspected physicians caring for patients with SE and RSE of being reluctant to prescribe ketamine as an AED. Our small survey of physicians sheds some important light on the views of ketamine for SE and RSE in Canada.

First, ketamine fails to appear in the management algorithms in the majority of physician respondents. When questioned about the first six AEDs used in SE, ketamine only appeared in 2.6%, 5.7%, and 6.1% of responses for fourth-, fifth-, and sixth-line AEDs. This potentially represents the lack of familiarity with the ketamine literature and discomfort with using NMDA antagonists in SE and RSE.⁵ In addition, the recent systematic review on this topic identified variable timing to implementation of ketamine in adults and pediatrics—16 hours to 140 days and 5 hours to 28 days, respectively. This highlights the current literature reports for ketamine as a salvage therapy in the most refractory of cases. This is further echoed in only 47.4% of respondents indicating having ever used ketamine for seizures in the past. Another reason for the lack of experience with ketamine via respondents is the lack of its mention in any guidelines for the managing SE or RSE.

Second, those respondents having used ketamine previously indicated that the majority of uses were in the neurological population, at 42.1%, with a mean number of two patients treated. The minority reported using ketamine for seizures in the neurosurgical population. We suspect this reflects the concerns arising from preexisting literature surrounding elevations in ICP and

reductions in cerebral blood flow with ketamine administration in this population. These concerns are relatively unsubstantiated, given that a recent literature review indicated Oxford 2b, GRADE B, evidence against ICP elevations with both ketamine infusions and bolus in the traumatic brain injury² and nontraumatic³ neurological population.

Third, reported seizure response to ketamine therapy was much lower than described in the literature. Our respondents indicated 10.3% complete seizure response rate. Similarly, only 13.8% and 37.9% reported a majority and minority of treated populations responding to ketamine therapy, respectively. A recent review indicates up to 56.5% and 63.5% of adult and pediatric patients, respectively, with RSE.⁵ Though difficult to determine from the responses, we suspect the lower rate of reported response is secondary to dosing, timing to ketamine administration, and potential pathology-specific resistance patterns. Furthermore, the addition of ketamine later in the disease course (ie, after multiple trials of other AEDs) has been displayed within the systematic review to correlate with a decreased response to the drug⁵ because of prolonged seizure duration and receptor changes. This may account for the poor seizure response reported in the survey. Finally, p-glycoprotein transporters have been documented to effect phenytoin and phenobarbital response; however, no such literature exists for p-glycoprotein's effect on ketamine transport and availability. Thus, it is possible that ketamine, though not documented in the literature to date, is indeed a substrate for p-glycoprotein or other transporters, and thus decreases its effectiveness in late application.

Fourth, the decision to implement ketamine as an AED was not made independently by the responding physician in the majority of cases. Only 27.6% independently reported prescribing ketamine for SE or RSE. Again, we suspect this stems from inexperience with the medication, concerns over ICP and cerebral blood flow response, and lack of exposure to existing literature on the use of ketamine in SE and RSE. This is exemplified by 75.8% of respondents indicating they view ketamine for SE and RSE as an experimental treatment. Similarly, only 45.2% indicated they were aware of the literature surrounding ketamine for seizures.

Finally, 67.9% of respondents would consider ketamine again for SE, with 48.3% considering it earlier in their treatment algorithm. Furthermore, 74.2% indicate willingness to participate in a prospective study evaluating early ketamine administration for SE and RSE. This was a surprising response, but exposes the potential excitement over NMDA antagonists for seizures and highlights the desire for novel therapies for SE and RSE.

Our study has limitations. First, we obtained a small number of responses to our survey despite lobbying the entire Canadian Neurological Science Federation and critical care departments across the country. It is unknown the exact number of critical care physicians in Canada currently practicing; however, gross estimates would suggest around 30 to 40 intensivists per province caring for patients in a tertiary care setting. Thus, our conclusions may not apply to the general population of physicians caring for

patients with SE or RSE. Furthermore, using ketamine for SE and RSE outside of North America is not known. Given the paucity of data on its use in the literature, as identified by the recent systematic review,⁵ it is suspected that the drug is typically reserved for the most refractory cases. Second, all survey responses contain the potential for reporting bias, and ours is no exception. Third, we used the term "refractory seizure" in the survey questions. Our intent was to identify those patients with SE or RSE treated with ketamine. This term may have been confused by some respondents and affected the final data collection on ketamine usage in Canada. Finally, we designed the survey for brevity and in doing so avoided questions surrounding dosing and duration of ketamine therapy in the past. Thus, specific comments on our respondents' experience with ketamine therapy cannot be made.

Despite these limitations, we believe our small survey has exposed some important points on the Canadian experience and views toward ketamine for SE and RSE. With the results of a recent systematic review on ketamine in traumatic brain injury² and as an AED,⁵ we believe the time has come to push forward with a prospective evaluation of early ketamine administration for patients with SE and RSE, and based on our respondents, many across the country are willing to participate.

Ketamine for SE and RSE has been sparingly used across Canada, with variable physician-reported response rates. We suspect preexisting literature has impeded the administration of ketamine in the neurological/neurosurgical population. Further prospective evaluation of early ketamine administration is warranted, and Canadian respondents are willing to participate.

DISCLOSURES

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SUPPLEMENTARY MATERIAL

To view supplementary material for this article, please visit <http://dx.doi.org/10.1017/cjn.2015.16>

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