Review Article

Ketamine — New Antiepileptic Drugs and Status Epilepticus

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ABSTRACT

Aim of review: Seizures are one of the most common neurological emergencies. For repeated seizures, the efficacy of traditional drugs is not ideal. Effective and timely treatment is necessary to terminate seizures and avoid brain function damage. Recent studies have found that ketamine has a better therapeutic effect.

Method: Recent articles and literature about ketamine use in the treatment of seizures were searched and reviewed, in order to identify therapeutic effect, drug dosage and its application in adult and pediatric patients.

Recent findings: Ketamine possesses special good points for the patients with status epilepticus who cannot be cured by traditional drugs. Seizure control upon ketamine administration in the adult population was documented as excellent (complete response in all patients involved) in studies. Seizure control in the pediatric studies was documented as also excellent. However, the timing of ketamine response was poorly documented in both the adult and pediatric studies. Most evidence show that the dose should include a bolus dose around 3mg/kg, since this is the median of the range described in the literature. Continuous infusion should follow ranging up to 10mg/kg/h, as this is the upper limit described. Finally, duration of treatment should be up to 7 days. Most patients reported in studies responded within 48 to 72 hours of ketamine initiation.

Summary: There were limited documents for the usage of ketamine for patients suffered from epilepsy. In the future, we need more clinical trials to validate its reliability and safety.

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It is well known that seizures are one of the most common neurological emergencies. Effective and timely treatment is necessary to terminate seizures and avoid brain function damage. The International League against Epilepsy (ILAE) defined a seizure as a transient occurrence of signs and/or symptoms due to abnormal excessive or synchronous neuronal activity in the brain. Seizures are usually brief and self-limited. Generalized tonic clonic seizures usually last less than 3 minutes (1-5).

As seizures are self-limited, there is no need for urgent treatment. However, once seizures exceed a certain duration, they are called status epilepticus (SE) and need to be managed as such.

Definition of Status Epilepticus, Refractory Status epilepticus and Super-Refractory Status Epilepticus

The 1981 ILAE definition of SE describes a seizure that "persists for a sufficient length of time or is repeated frequently enough that recovery between attacks does not occur" (6). The absence of a definitive timeframe of seizure duration creates ambiguity, which makes it

difficult to accurately define and treat SE. Accordingly, SE was redefined as a seizure lasting 60 minutes, then further refined by the Epilepsy Foundation to a seizure lasting 30 minutes on the basis of estimates of the time needed to sustain neuronal injury from a prolonged seizure (7).

On the basis of evidence of typical seizure duration, animal data of neuronal injury, and data of pharmaco-resistance, an operational (as opposed to mechanistic) definition of SE stipulates the treatment of convulsive SE within 5 minutes of seizure onset (5, 8). This definition can also be extended to other forms of SE, including focal SE with dyscognitive features and absence SE. At present, the ILAE is considering a proposal of a more practical operational definition of SE that emphasises early identification and treatment. This new definition emphasises two critical time points: the duration of the seizure and the time at which a prolonged seizure could lead to long-term consequences, including neuronal injury and cell death.

SE is relatively common, with estimates of 50,000-60,000 new cases annually in the USA (9, 10). The incidence of SE in Europe is somewhat lower (10-16 per 100,000 population) (11) compared with the USA (18-41 per 100,000 population). Notably, American ethnic minorities have a substantially higher incidence (57 per 100,000) than the Whites (20 per 100,000) (12). Results of trend studies (13, 14) showed an increase in incidence of SE in the past few decades in the USA. Findings from a study (9) of first episodes of SE showed that the majority (54%) of cases occur in the absence of a known diagnosis of epilepsy. When associated with epilepsy, SE tends to occur early in the course of epilepsy, representing the first or second unprovoked seizure 65% of the time. SE also confers an increased risk of future seizures, with a 3.3-times higher risk of a subsequent unprovoked seizure after symptomatic SE when compared with the risk following a single, self-limited, symptomatic seizure (15).

The pharmacological management of repetitive seizures and SE still represents an area with limited robust evidence derived from high-quality, adequately powered randomized controlled trials (RCTs) to inform clinical practice. Most evidence in this topic regards to the treatment of early SE, which has been the subject of several RCTs and critical assessment in systematic reviews and meta-analyses (16-23) and included in treatment protocols or practical guidelines (24-27). All treatment protocols recognize a staged approach to treatment with different drugs used in early (stage I), established (stage II), refractory (stage III), and super-refractory SE (stage IV). All treatment protocols emphasize prompt recognition and treatment of persisting seizure activity at each stage to prevent death or irreversible brain damage and reduce morbidity and mortality.

Refractory status epilepticus (RSE) refers to SE that cannot be resolved in terms of clinical manifestations or epileptiform discharges following the rational administration of anticonvulsants including benzodiazepine (28). Super-refractory status epilepticus (SRSE) refers to drug-resistant SE that persists or recurs following the continuous administration of intravenous anesthetics for more than 24 hours (29), and the primary etiologies of SRSE are brain insults, such as intracranial infection, brain trauma or stroke (29, 30). When the seizure duration exceeds 30 minutes, the mortality rate is 19% (31). Among RSE patients, the mortality rate is as high as 23-61% (26, 27), and approximately 90% of RSE survivors ultimately relapse (31-33). Ketamine could play an important role in the treatment of RSE/SRSE by altering glutamate metabolism, particularly in patients who exhibit a poor response to benzodiazepines.

Use of Ketamine for Seizures

Ketamine was discovered in 1962. It is on the World Health Organization's List of Essential Medicines, of the most important medications needed in a basic health system. Ketamine has a strong antagonistic effect on the N-methyl-D-aspartate (NMDA) glutamate receptor, and has a half-life of 2-3 hours, which is extensively metabolized by hepatic cytochrome P450 pathway to active metabolite, norketamine.

There is a small amount of literature reviews on the use of ketamine as a treatment for refractory SE. Most of the data to date focuses on small case series reported retrospectively. Results with the utilization of NMDA antagonists are promis-

ing even in the most refractory of cases of SE.

Adults

Within 9 studies about ketamine use for seizure control in the adult population (34-42), some researches utilized bolus dosing of ketamine (ranging from 0.5 to 2 mg/kg), followed by continuous infusions (ranging from 0.05 to 7 mg/kg/h) (Table). The remaining studies utilized only bolus dosing in five and it was unknown about ketamine administration detail in one. Duration of treatment prior to ketamine administration was documented in the studies, ranging from 16 hours to 140 days, with patients on various numbers of antiepileptic drugs (AEDs) prior to ketamine, ranging from 1 to 11, with all patient-directed treatments typically consisting of a combination of oral AEDs and intravenous anesthetic agents. All AEDs reported were typically on board during the ketamine treatment. Similarly, the duration of ketamine treatment was described in the adult studies, with treatment duration ranging from 2 hours to 27 days intravenously, and one patient discharged on oral ketamine indefinitely (42).

Seizure control upon ketamine administration in the adult population was documented as excellent (complete response in all patients) in studies containing a total of the patients. Moderate electrographic seizure response (> 50% of patients in the study responded) was documented in two studies with a total of 16 patients. Mild electrographic seizure response (<50% of patients in the study responded) was documented in one study with 46 patients. Failure of treatment response in all patients occurred in three studies with a total of 12 patients. Across all adult studies, a total of patients (56.5%) were described as having complete electrographic seizure responsiveness to ketamine. Complete treatment failure with ketamine was described in 51 (46.4%) adult patients across all adult studies. The timing of ketamine response after administration was poorly documented within the majority of the adult studies.

Pediatrics

Within those studies describing the use of ketamine in the pediatric population, one study doc-

Table. Ketamine-Related Studies About Treatment Eharacteristics, Seizure Response, and Outcome

Studies	The number of patients	Dosing range	Outcome
Hsieh et al. (34)	1	Bolus: 0.5 mg/kg Infusion: 1.5 mg/kg/h	Control
Kofke et al. (35)	1	Bolus: 150 mg × 4 Infusion: 0	Control
Kramer et al. (36)	1	Bolus: 50 mg × 4 Infusion: 0.6-3.3 mg/kg/h	Control
Prüss et al. (37)	1	Bolus: 0.5 mg Infusion: 0.4-3.2 mg/kg/h	Control
Walker et al. (38)	1	Bolus: 0 Infusion: 100 mg/h	Control
Robakis et al. (39)	1	Infusion: up to 7 mg/kg/h	Failure
Synowiec et al. (40)	11	Bolus: 1.3 mg/h Infusion: 100 mg/h	Control
Ubogu et al. (41)	1	Bolus: 2 mg/h Infusion: 1-7.5 mg/kg/h	Control
Yeh et al. (42)		Bolus: 1.5 mg/h Infusion: 0.05-4 mg/kg/h	Control

umented bolus dosing, ranging from 2 mcg/kg to 3 mg/kg, followed by continuous intravenous infusions, from 7.5 mcg/kg/h to 10 mg/kg/h. In the other studies, isolated continuous infusions of ketamine was documented in two studies, ranging from 7 to 60 mcg/kg/min, oral dosing was documented in one study (43), and not documented in other 3 studies (44). Duration of treatment prior to ketamine administration was documented in 2 pediatric studies, ranging from 5 hours to 28 days, with patients on various numbers of AEDs prior to ketamine, ranging from 1 to 10 with all patient-directed treatments typically consisting of a combination of oral AED and intravenous anesthetic agents. All AEDs reported were typically on board during the ketamine treatment. Similarly, the duration of ketamine treatment was described in 4 patients, ranging from 6 hours to 27 days. The timing of ketamine response was poorly documented in the pediatric studies. Seizure control in the pediatric studies was documented as also excellent.

Special Cases Patients

Tarocco et al. (45) presented a case report of use of ketamine administered to a late preterm with Pierre Robin sequence, lissencephaly, polymicrogyria, and severe epilepsy. A dose of MDZ up to 20 mcg/kg/min was needed to obtain transient seizure control. The addition of levetiracetam

up to 50 mg/kg/d did not inhibit the seizures, which were controlled only by propofol at the dose of 2 mg/kg. As suggested by the pediatric neurology staff of the Meyer Children′s Hospital in Florence, they started intravenous ketamine: two boluses of 2 mg/kg immediately followed by continuous infusion of 10 mcg/kg/min, obtaining immediate, complete clinical, and electrographic response. In the next 12 days, they needed to increase ketamine up to 24 mcg/kg/min, with occasional boluses of 2 mg/kg to maintain complete clinical and electrographic response and to allow extubation. After 15 days without seizures, SE reappeared, the patient's general clinical state deteriorated, in spite of ketamine increased to 60 mcg/kg/min, and the patients died finally. Diagnosis of the complex syndrome presented by this newborn is being pursued. When first- and second- line AEDs fail, continuous IV anesthetics are often initiated. That is to say, ketamine is considered in the late phase of treatment.

But the view of Zeiler et al. (46) is that consideration should be given for the early use of ketamine in refractory SE because of the report (45). Two patients who underwent elective aneurysm clipping developed medically refractory SE post-craniotomy. No structural, vascular, infectious, or metabolic cause was identified. Seizure control failed with multiple medications and intravenous sedatives over the period of weeks in both. Ketamine was instituted at 20 and 40 mg/kg/min in these patients. Within hours of starting ketamine, burst suppression was obtained in both. Medications were all tapered over the next month, and both the patients recovered to be cognitively normal, with mild residual morbidity secondary to critical care polyneuropathy.

The main difference between these two patients is the time point that ketamine was used, the usage of ketamine was on post-operative day 17 (12 days after seizure onset) for the first patient and post-operative day 4 (4 days after seizure onset) for the second patient. The author thought the initial experience in case 1 prompted early initiation of ketamine in case 2, whereas without this prior success, they may have waited longer to start such a nonconventional therapy.

In fact, the timing of initiation of such nonconventional AED (anti-epileptic drugs) is controversial. One major question arose from the review and still remains now: Would ketamine/NMDA receptor antagonists be more effective if utilized earlier in RSE/SRSE? The simple answer is that they do not know. However, one could extrapolate that with the reasonable success obtained in the cases summarized in the systematic review and earlier implementation of NMDA receptor antagonism, less glutamate mediate excitotoxicity would occur, and potentially SE will be less refractory. This has yet to be seen. Why not utilize ketamine/NMDA receptor antagonists earlier in RSE/SRSE? It is difficult to find one good reason not to. When should they try these drugs in RSE/SRSE? Is it potential after the failure of the initial benzodiazepine and phenytoin load? Is it considered after the failure of the initial intravenous sedative agent? This is still up for debate.

Sabharwal et al. (46) used ketamine in some patients with SRSE. The retrospective chart review included 67 patients with ages ranging from 8 to 85 years old (mean age: 58 years old, median age: 62 years old) over a period of 4 years(2012- 2015). Ketamine was the initial agent used in 6 patients (9%). The dose range was 25- 175 mcg/kg/min. The duration ranged from 1 to 29 days with a mean duration of 6.0 days. Propofol was the initial agent used in 61 patients (91%). The dose range was 25-140 mcg/kg/min. The duration ranged from 1 to 34 days with a mean duration of 6.5 days. The duration of combined ketamine and propofol use ranged from 1 to 28 days (mean time: 6 days). Infusion rates ranged up to 145 and 175 mcg/kg/min. Vasopressors were used in 53 patients (79%), and were given within the first 5 days of the intensive care unit (ICU) admission in 48 (91%) patients. The overall SRSE resolution rate was 91% , and the overall mortality including patients with anoxic brain injury was 39%. Of the 13 patients with SRSE as a result of anoxic brain injury, SRSE was controlled in 5 (56%) patients. The primary determinant of mortality was family withdrawing care related to the presence of severe medical/neurological diseases. According to the author, the use of ketamine infusions early in the management of SE has recently been proposed because of its favorable seizure resolution rate and hemodynamic/complication profile.

Non-Antiepileptic Effect and Adverse Effects

Neuroinflammation is currently considered as one of the mechanism that can be responsible for epileptogenesis, although some experimental data suggest that it is not a sine qua non condition (47). Ketamine is known to exert anti-inflammatory effects (48). Dhote et al. (49) recently brought evidence that it could also considerably limit soman- induced neuroinflammation, although this could be the result of the arrest of seizures.

Compared with other drugs used for the treatment of SE, ketamine- induced respiratory depression is rare in humans but has a higher occurrence in rodents. Other NMDA antagonists share this property. This side effect can be effectively prevented by muscarinic antagonists like atropine (50-54) in conditions when the precipitating event may favor respiratory depression, during nerve agent poisoning for instance. The increased bronchial secretions can also easily be reduced with atropine.

Only two patients in the adult literature reviewed were described as having cardiac arrhythmias directly related to ketamine administration. Within the pediatric literature, one study (55) described hyper- salivation in 9 patients and elevated liver enzymes in one patient with phenobarbital administration at the time. No other adverse effects/complications described in the adult or pediatric studies were directly attributable to ketamine administration.

Dosing Range of Ketamine

On basis of the studies identified in the review, ketamine is the NMDA receptor antagonist medication to implement currently. Most evidence show that the dose should include a bolus dose around 3mg/kg, since this is the median of the range described in the literature. Continuous infusion should follow ranging up to 10mg/kg/h, as this is the upper limit described. Finally, duration of treatment should be up to 7 days. Most patients reported in studies responded within 48 to 72 hours of ketamine initiation. However, there are some extreme cases, the beginning dose of infusion was at 40 mg/kg/min and maintained 12 days.

Possible Mechanism of Ketamine

The majority of current AEDs work via GABA, sodium channel, or calcium channel mediated mechanisms(26), as previously outlined. Given the aforementioned alterations in cerebral receptor and transporter functions in RSE/SRSE, in addition to the non-receptor mediated mechanisms of pharmaco- resistance, the efficacy of the majority of AEDs is impacted, and thus there exists a need for novel therapeutic targets. Targeting the NMDA receptor provides such a novel approach. The use of NMDA receptor antagonists for SE, such as ketamine, provides a few benefits. First, NMDA receptor antagonists target a receptor known to be upregulated during SE/RSE/SRSE and one that contributes to excitotoxicity (56- 59). Second, NMDA receptor antagonists provide a degree of neuroprotection even after SE (57- 59). This neuroprotective effect has even been studied within the traumatic brain injury literature (57, 58). Third, in regard to ketamine, this drug is readily available and cheap, allowing for application in a variety of settings. Fourth, the sympathomimetic properties of ketamine in particular afford it vasopressor sparing effects, which reduce the need for vasoactive compounds to counteract the hypotension commonly seen with other intravenous anesthetics used in SE. Fifth, the side effect profile in the neurological population, as documented in the literature to date, is low despite some initial concerns about potential neurotoxicity. Recently, the hyperpolarization-activated cyclic nucleotide channels (HCN1 channels) have been found to contribute to the sedating actions of ketamine (60, 61), which may be an favourable factor for the control of SE.

Conclusion

Ketamine possesses a wide range of positive assets to become a more traditional way of treating SE. Numerous questions remain, and in absence of RCTs, the medical community will have to rely mostly on preclinical studies. The long list of unanswered questions will require extensive research, and this will be best achieved by cross talks between the research communities interested in epileptic seizures and SE on one hand and in nerve agent poisoning on the other hand.

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