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Research Article

Ketamine in Refractory and super-refractory seizures: a Retrospective Observational Study

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Abstract

Introduction: Super-refractory status epilepticus refers to drug-resistant status epilepticus that persists or recurs following the continuous administration of intravenous anesthetics for more than 24 hours or when tapered after 24 hours. Ketamine could play an important role in terminating such seizures.

Methodology: This retrospective observational study was conducted in a tertiary care Neurosciences hospital of eastern India. Records of patients of refractory status epilepticus (SE) who received ketamine and underwent scalp EEG/ continuous EEG in the intensive therapy unit were reviewed and their clinical, detailed treatment and investigation records were analysed. Records of patients admitted from 2019 to 2023 with a diagnosis of super-refractory status epilepticus (SRSE) were screened. There were 14 cases of SRSE who received ketamine infusion. Seizure control (both clinical and/or electroencephalographic), cardiovascular and intracranial haemodynamic parameters, and final outcome of the patients were analysed.

Results: Majority had new onset SE of varying etiology and were treated with antiseizure medications prior to anesthetic drug administration. The median ketamine infusion dose was 5mg/kg/hr and duration ranged from 1-30 days. All required mechanical ventilation and 71.4% were on vasopressor support. Combination of ketamine and low dose midazolam effectively suppressed epileptic discharges and improved haemodynamic stability in 42.9 % cases. Except for two patients who had associated sepsis, the rest had a favorable outcome.

Conclusion: This study has generated data about the effectiveness and safety of ketamine in controlling seizures in a cohort of SRSE patients. However, further studies are required to establish its efficacy and safety.

Keywords: Super Refractory Status Epilepticus; Ketamine; Effectiveness; Safety; Observational Study

Introduction

Refractory status epilepticus is defined as status epilepticus (SE) which cannot be controlled in terms of clinical manifestations or epileptiform discharges following the administration of benzodiazepines (midazolam, lorazepam and alike) and anticonvulsants (phenytoin, fosphenytoin, valproate, levetiracetam and alike) [1]. Super-refractory status epilepticus (SRSE) refers to drug-resistant status epilepticus that persists or recurs following the continuous administration of intravenous anesthetic agents for more than 24 hours or when tapered after 24 hours [2]. The reported death rate is approximately 19% in cases where the length of the seizure duration exceeds 30 minutes [3] and the prevalence is 23-61% in patients with RSE [4]. Anesthetic medications, which have side effects of their own, are frequently needed for treatment.

Because it modifies glutamate metabolism, ketamine may be useful in treating SRSE, especially in patients who do not respond well to benzodiazepines.

The quantity of GABA (gamma aminobutyric acid) A receptors on postsynaptic receptors decreases with prolonged seizures, but the quantity of inactive GABA-A receptors increases [5,6]. The efficacy of antiepileptic medications that target the GABAergic system is significantly reduced as a result of these modifications. AEDs may become more effective at higher doses; however such high doses are frequently linked to negative effects on cardiopulmonary function, which restricts their use in clinical settings. It has been observed that as GABA receptor activity declines, glutamate-sensitive N-methyl-D-aspartate (NMDA) receptor numbers and activities rise [7]. Neurotransmission is blocked by the NMDA receptor antagonist ketamine [8,9]. Consequently, it has been suggested as a novel therapeutic agent to treat status epilepticus [10-12]. We used ketamine in refractory status epilepticus in few patients in the intensive therapy unit of our hospital.

Methods

Cases of RSE and SRSE treated with intravenous ketamine from 2019 to 2023 were retrospectively identified from hospital records. Their clinical, pharmacy records and investigation reports were reviewed.

Data were collected using a study specific data extraction form and all variables including loading dose, maximum infusion rate, duration of infusion for all antiseizure drugs administered and outcomes (clinical and electroencephalographic) were collected. Anesthetic drugs included midazolam, propofol and ketamine. Control of SE was defined as cessation of clinical, electroencephalographic ictal manifestations and burst suppression as ascertained by continuous video-EEG monitoring (4 cases) or clinical evaluation and intermittent EEG. Adverse events were attributed to ketamine if they occurred after initiation of ketamine and if they led to lowering of the dose or discontinuation.

Results

Amongst 14 cases of RSE, most of the patients had new onset refractory status epilepticus of unknown etiology. Table 1 depicts the patient characteristics, seizure etiology, type and the duration. We have observed that the median age was about 49 years with male preponderance. Table 2 summarizes the details of ketamine used for RSE management. The loading dose was 2mg/kg followed by a continuous infusion 2-8 mg/kg/hr (median 5mg/kg/hr). Ketamine was a part of a multi-drug regimen for super refractory status epilepticus. The duration of ketamine infusion ranged from 1 to 30 days.

Age in yr; median (range)	**48.6 (21-71)**
Gender (%)	
male	8 (57.1)
female	6 (42.9)
Etiology n (%)	
NORSE	7 (50)
Intracranial haematomas	4 (28.57)
Brain tumour	1 (7.14)
Arterial territory infarct	1 (7.14)
Known seizure disorder	1 (7.14)
Duration of SE in days; median (range)	4 (1-30)
Classification of SE n (%)	
generalized convulsive	9 (64.28)
tonic-clonic	6 (42.9)
myoclonic	2 (14.28)
tonic	1 (7.14)
focal convulsive	2 (14.28)
non convulsive status epilepticus	3 (21.42)

Table 1: Patient and seizure characteristics (14 cases of SRSE).

Parameter	**Median (Range)**
Latency to ketamine (days)	4 (0.5-13)
Duration of ketamine administration (days)	4 (1-30)
Loading dose of ketamine (mg/kg)	2
Maximum infusion rate of ketamine (mg/kg/hr)	5 (2-8)
Number of concurrent antiepileptic drugs	6 (4-8)
Number of previously failed drugs	5 (4-8)
Number of concurrent anaesthetic drugs	1.5 (1-2)

Table 2: Usage of ketamine.

There were no specific drug combinations that improved response to ketamine. But timely combination of ketamine and low dose midazolam effectively suppressed epileptic discharges and improved haemodynamic stability in 42.9% (6 out of 14 cases). The overall mortality rate was 14.3% (2 out of 14 cases). Dose and duration of exposure to ketamine were not related to mortality.

Analysis of the trend in seizure control showed that 3 patients had seizure control within 24 hours of ketamine initiation while another 3 had seizure control within 48 hours of ketamine initiation. None of the patients had seizure after ketamine discontinuation, thus all had responded to ketamine.

The two patients who succumbed had achieved seizure control but succumbed to sepsis.

The mean dose of midazolam when ketamine was initiated was 0.19 mg/kg/hr.

Analysis of the effects of ketamine on MAP revealed that in 5 patients, nor-adrenaline support requirement did not decrease after starting ketamine, while in the others, they were hemodynamically stable and there was subsequent decrease in the requirement of vasopressors/no need of vasopressors. None of the patients had increase in ICP while on ketamine infusion as evidenced by optic nerve sheath diameter (ONSD) values by ultrasound (Table 3).

S. No.	ONSD during admission	ONSD during the maximum dose of ketamine
1	4.8	4.8
2	5.0	4.9
3	4.7	4.8
4	5.2	5.2
5	4.6	4.5
6	5.1	5.1
7	5.3	5.2
8	4.9	4.8
9	4.5	4.6
10	4.6	4.6
11	5.0	5.1
12	5.2	5.0
13	5.4	5.3
14	5.1	5.1

Table 3: ONSD values (in mm)– an indirect assessment of intracranial pressure.

All patients required mechanical ventilation and 71.4 % (10 out of 14 cases) required vasopressors. Among these 10 patients, 5 patients had infections and features of sepsis and so required vasopressors, of whom the vasopressor requirement increased even after starting ketamine in 2 patients and they ultimately died. The remaining 5 patients had hypotension due to the administration of midazolam/propofol and the requirement of vasopressor reduced on starting ketamine infusion.

We reviewed all the treatment records for detecting any known treatment emergent adverse effects of ketamine. There were no features or investigational reports suggestive of ketamine induced liver injury i.e. rise of liver enzymes > 3 times upper limit normal or raised serum bilirubin level. We also did not find any evidence of cardiac rhythm disorders like supraventricular arrhythmias while the patients were on ketamine. One patient had dissociative symptoms due to prolonged administration of ketamine, thus the dose was reduced and gradually tapered off in that patient and the symptoms resolved.

Discussion

This observational, single centre study has provided data on the use and effectiveness and safety of intravenous ketamine in a cohort of SRSE patients. 50% of the patients had new onset refractory status epilepticus of unknown etiology (NORSE) which has a poor prognosis compared to those with an identified cause. The NORSE patients received corticosteroids, immunotherapy and other anti-epileptics (levetiracetam, lamotrigine, clobazam, phenobarbitone and perampanel) along with ketamine and it was found to be effective in seizure control. In the group of patients who had previous documented history of seizure disorder, 4 had intracranial haematomas, one each had a meningioma and left sided posterior cerebral arterial territory infarction. Seizures were controlled in these patients with the administration of ketamine when conventional anti-epileptics failed to terminate them. In our study, we found that timely administration of ketamine achieved epileptic suppression in 12 cases, while 2 had succumbed to sepsis. It also reduced the dosage of midazolam and thus improved haemodynamic stability in 42.9 % cases.

We compared our study results with other published studies globally. Usually, an infusion dose of 1.5 to 10 mg/kg/hr is titrated to suppress electroencephalographic seizure discharges after a loading dose of 2 mg/kg [13]. The ideal dosage has not yet been

established [13]. Alkhachroum A., *et al*. [14]. study, conducted in Canada, assessed 68 SRSE patients who were receiving ketamine infusions retrospectively. About 55% of the individuals in the research showed a decrease in seizure frequency within 24 hours of ketamine treatment. The mean ketamine dose was 2.2 ± 1.8 mg/kg/h, and the median duration was 2 days. In our study the median dose of ketamine infusion was 5mg/kg/hour which was higher compared to the above study. Similarly the duration of ketamine infusion in our study was larger compared to the Canadian study. However the mean dose and duration of midazolam when ketamine infusion was initiated was comparable.

With respect to the effects of ketamine infusion on hemodynamic parameters our results were comparable as it reduced vasopressor requirements in majority of the patients and there were none who had developed raised ICP.

Ketamine was reported to be effective in a 2014 systematic review of NMDA receptor antagonists for the treatment of RSE [15]. An early combination of ketamine and low dose midazolam effectively controlled epileptic episodes and restored hemodynamic stability, according to a case series [16]. A single-center retrospective study [17] also revealed that ketamine was a useful medication for RSE/SRSE and that it might be more helpful when given sooner or for a longer period of time, in addition to when combined with benzodiazepines. Gender SS., *et al*. reported two cases [18] of SRSE with septic shock who were administered ketamine infusion 36 and 24 hours respectively after initiating and escalating midazolam infusion with resultant decrease in epileptiform activities, clinical improvement and decrease in requirement of vasopressors.

There is a lack of information on ketamine's therapeutic dosage or application in the treatment of status epilepticus.

It was demonstrated in a case series published in 2012 [19] that dosages up to 7.5 mg/kg/hr taken for up to 14 days were safe. According to a different case study by Gaspard N., *et al*. [20], dosages up to 10 mg/kg/hr for a maximum of 27 days were deemed safe. In our study administration of doses upto 8 mg/kg/hr for upto 14 days was not associated with increased complications or mortality compared to patients receiving lower doses and shorter duration of exposure. The 14.3 % mortality was due to presence of systemic infections and the patients succumbed due to sepsis related complications.

A case was reported [21]. where an 18 year old college student presented with intractable seizures following ingestion of synthetic marijuana, he responded to ketamine bolus 1 mg/kg bolus followed by infusion 2 mg/kg/hr after failure of conventional anti-epileptic drugs, midazolam and thiopentone infusion.

Guidelines have highlighted the role of general anaesthesia as the standard therapeutic approach for refractory status epilepticus, though this evidence mainly comes from uncontrolled studies. In majority of the published cases, anaesthetics were used as a third-line or fourth-line agent.

Thus, the efficacy of ketamine in our series is similar to that of other anaesthetic agents.

Analysis of safety of ketamine infusion in SRSE patients showed that common psychiatric adverse effects were hallucinations, delirium, dreams and blurred vision [22]. In our study, only one patient developed dissociative symptoms due to prolonged administration of ketamine and it subsided when the drug was tapered off.

It has been reported that the adverse reactions related to ketamine were rare. In our study no patient had increase in intracranial pressure (ICP) which was similar to that reported by Mayberg., *et al*. in 1995 [23]. Another publication where ketamine was used for nontraumatic neurological diseases also did not observe any increase in ICP and in some cases, they found that ketamine even reduced ICP [24].

Limitations

The limitations of our study include those that are inherent of retrospective observational studies. Additionally, there was variability in the prescribing trends as it was based on clinical judgment of various treating clinicians. Finally as we did not do a multivariate analysis due to small sample size the effects of concomitant antiepileptics and anaesthetic drugs on seizure control could not adjust for the effects of these agents.

Despite these limitations, this study documents the utility and patterns of administration of ketamine for the treatment of refractory and super-refractory status epilepticus.

Conclusion

The treatment of RSE and SRSE is quite challenging and early initiation of appropriate antiepileptic drugs is important. Continuous

ketamine infusion appears to be safe and efficient in suppression of epileptiform discharges and provided haemodynamic stability when used with other anesthetic agents for the treatment of RSE and SRSE. But there is lack of prospective randomized studies on the efficacy of ketamine and hence recommendations cannot be made. Thus further studies are required to investigate the role of ketamine in RSE and SRSE.

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Conflict of Interest

Nil.

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