EFFICACY AND SAFETY OF KETAMINE FOR THE MANAGEMENT OF REFRACTORY STATUS EPILEPTICUS (RSE) IN ADULTS

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ABSTRACT

Objective: To determine the efficacy and safety of ketamine (KE) in the management of refractory status epilepticus (RSE) in adults.

Study Design: Open Label, unblinded prospective case series.

Place and Duration of Study: The study was conducted at Neurology Department Military Hospital Rawalpindi, from Jan 2014 to Dec 2014.

Material and Methods: All the patients with status epilepticus, from Jan 2014 to Dec 2014 were treated with ketamine in addition to benzodiazepines, phenytoin and levitricetam. Ketamine was the last drug added and if seizures were still not controlled then anesthetic agents like thiopental and propofol were used.

Results: Between Jan 2014 and Dec 2014, twenty patients received IV Ketamine. In 18 patients RSE lasted for more than 24 hours, with a median of 4 days (range 1-8 days). Mean duration of seizures in the study group was 4.45 days (SD 2.01). Ketamine was successful in terminating seizure activity in 40% (n=8) patients while it failed in 15% (n=3) patients. There was additional 15% (n=3) partial response in the form of initial control but these patients had later breakthrough or with drawl seizures. Twenty five percent (n=5) of the patients died during the treatment while in one patient ketamine had to be stopped because of intolerable side effects. In our patients the adverse effects of ketamine included sepsis (35%, 5, n=7), shock (10%, n=2) and pneumonia (10%, n=2).

Conclusion: In this small, open-label, unblinded study KE appears effective and safe in treating RSE in adults. Larger, randomized studies will help to confirm data emerging from this preliminary study.

Keywords: Ketamine (KE), refractory status epilepticus (RSE), status epilepticus (SE).

INTRODUCTION

Status epilepticus (SE) is an epileptic seizure of more than five minutes or more than one seizure activity within a five minute period without the person coming back to state of health in between them. The seizures can either be of the tonic-clonic type or of other types that do not involve muscle contractions such as absence seizures or complex partial seizures[1]. The annual incidence of status epilepticus (SE) is 10–40/100,000 and it is the second most common neurological emergency (acute stroke being the first)[2]. Refractory status epilepticus (RSE) is defined as failure to respond to appropriate doses of two antiepileptic drugs one of them being benzodiazepine[3]. SE is a major medical and neurological emergency and is associated with high mortality and morbidity[4]. The termination of RSE frequently requires anesthetic drugs, which can be associated with lethal complications. Many a time, patients have to be intubated and mechanically ventilated to terminate status epilepticus and it is associated with bad prognosis. Different antiepileptic drugs can be used for the management of status epilepticus with varied pharmacological properties. The mechanism of action of lorazepam, diazepam, and phenobarbital is to enhance activation of gamma-aminobutyric acid agonist (GABAA) receptors. In contrast, phenytoin stabilizes the inactivated state of sodium channels there by limiting sustained repetitive firing of neurons[5]. Prolonged seizures are accompanied by a decline in sensitivity to GABA agonists, which results in progressive decrease in the efficacy of these anti epileptics[6].

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Received: 01 Mar 2016; revised received: 18 Apr 2016; accepted: 04 Nov 2016

Such decline in the sensitivity has not been associated with N-methyl-D-aspartate (NMDA) antagonists that is another class of antiepileptics[7]. Ketamine is an NMDA antagonist and it can potentially be used for the management of refractory status epilepticus (RSE). Many animal studies have shown efficacy of ketamine for control of RSE[8]. Ketamine has also been used for the treatment of RSE in humans in the last several years but most published data has been presented in case reports or small series[9]. A recent systematic review of all the literature pertaining to ketamine and seizure control was performed by Zeiler et al[10]. This review showed that across all studies, of the 110 adult patients described, ketamine administration resulted in electroencephalogram seizure response in 56.5%. Adverse events related to ketamine were rare. There is current Oxford level 4, GRADE C recommendation for the use of ketamine for refractory seizures in the adult and pediatric populations[10]. The purpose of this study was to document the experience with intravenous (IV) ketamine in the treatment of RSE in our hospital.

MATERIAL AND METHODS

This study was carried out at Neurology Department of Military Hospital, Rawalpindi from Jan 2014 to Dec 2014 for a total duration of one year. Twenty patients with the diagnosis of refractory status epilepticus (RSE) were included in the study. All the patients were managed in the Intensive Care Unit (ICU) of this hospital. Permission from hospital ethical committee was obtained prior to start of the study. A written informed consent was also obtained from all the patients included in the study.

Status epilepticus (SE) was defined as epileptic seizure of greater than five minutes or more than one seizure within a five minute period without the person coming back to normal health state in-between them. Refractory status epilepticus (RSE) was defined as failure to respond to appropriate doses of midazolam, phenytoin and levetricetam. All the patients with RSE were treated with ketamine (KE). A loading dose of 5mg/kg was given followed by continuous infusion of 5mg/kg/hr. The response to therapy was assessed clinically and was categorized as under;

- **Successful Therapy**: The status epilepticus was completely terminated by the therapy, without breakthrough seizures, or discontinuation due to side-effects, or death during the therapy.
- **Initial Failure**: The KE administration failed to control status epilepticus at all.
- **Breakthrough Seizures**: Recurrence of status epilepticus during the treatment although it was controlled initially, resulting in the need for a change of therapy.
- **Withdrawal Seizures**: Recurrence of status epilepticus during or after decreasing the KE dose or withdrawal of the therapy, resulting in the need to restart or change of therapy.
- **Intolerable Side-Effects**: The therapy resulted in side-effects necessitating alternative therapy.
- Death during the course of the treatment[11].

Successful therapy was further divided in two categories; likely successful if KE was the last drug added before cessation of seizures and possibly successful if KE was part of the regimen which resulted in cessation of seizures. If seizures were still not controlled within 24 hours of starting KE then anesthetic agents were used including thiopental and propofol and patients were intubated and mechanically ventilated if required. Adverse effects were attributed to KE only if they occurred after the initiation of KE and if they lead to a lowering of the dose or discontinuation of KE. Data for each patient was entered on a patient's Proforma by the researchers. Data was analyzed using statistical package for social sciences SPSS version 17. Descriptive statistics were calculated for both qualitative and quantitative variables. Frequencies and percentages were calculated for qualitative variables like gender, etiology of epilepsy, previous history of epilepsy, type of SE, response to KE, use of mechanical ventilation and vasopressors and side effects. Mean and standard

deviation were calculated for quantitative variables like age and duration of seizures.

RESULTS

A total of twenty patients were included in this study. Out of them eleven were males and nine females. Mean age was 52.8 (SD ± 18.32) years. In 18 patients RSE lasted for more than 24 hours, with a median of 4 days (range 1-8 days). More than half of the patients (55%, n=11) had an unknown etiology for SE, while other causes were anoxic brain injury (10%, n=2), non anoxic brain injury and systemic causes (20%, n=4), remote symptomatic epilepsy (15%, n=3). Non-anoxic brain injury and systemic causes included meningo-encephalitis (n=1), subarachnoid hemorrhage (n=1), ischemic stroke (n=1) and traumatic brain injury (n=1) (table-I).

There was previous history of seizures in seven (35%, n=7). Mean duration of seizures in the study group was 4.45 days (SD ± 2.01). Different types of seizure activity observed were generalized convulsive (65%, n=13), generalized

Table-I: Response to Ketamine.

Response to Ketamine	Frequency	Percentage (%)
Successful	8	40.0
Failure	3	15.0
Breakthrough seizure	1	5.0
Withdrawl	2	10.0
Intolerable side effects	1	5.0
Death	5	25.0
Total	20	100.0

Table-II: Determinants of ketamine efficacy.

		Successful	Not successful	*p*-value
Sex	Male	9	2	0.102
	Female	4	5	
Etiology	Unknown	9	2	0.08
	Anoxic brain injury	1	1	
	Non anoxic brain injury and systemic causes	2	2	
	Remote symptomatic	1	2	
Type of seizure	Generalized convulsive	13	0	<0.001
	Generalized non-convulsive	0	1	
	Focal convulsive	0	5	
	Focal non-convulsive	0	1	

Table-III: Variables associated with mortality.

		Alive	Dead	*p*-value
Mechanical ventilation	Yes	14	5	0.75
	No	1	0	
Vasopressors use	Yes	6	2	0.693
	No	9	3	
Side effects	Yes	7	4	-
	No	8	1	

nonconvulsive (5%, n=1), focal convulsive (25%, n=5) and focal non-convulsive (5%, n=1). KE was successful in terminating seizure activity in 40% (n=8) patients while it failed in 15% (n=3) patients completely (table-II). The drug was likely responsible in 7 patients as it was the last drug added and possibly responsible in one patient as propofol was added after KE to control seizure activity. There was additional 15% (n=3) partial response in the form of initial control but these patients had later breakthrough or withdrawl seizures which were then controlled by using anesthetic agent propofol. Twenty five percent (n=5) of the patients died during the treatment while in one patient KE had to be stopped because of intolerable side effects. The overall mortality was 25% (5/20). There was no statistically significant relationship between KE use and mortality. Most patients (95%) were mechanically ventilated before administering KE and vasopressors were used in 8/20 patients (table-III).

DISCUSSION

This prospective case series showed that KE is quite safe and effective for termination of SE in adult population. In our study group it was effective in termination of SE in 40% of the studied patients and transient control was also achieved in another 15% without major side effects. Our study results are in line with some of the international studies which have shown ketamine to be equally or more effective in terminating RSE e.g Ketamine terminated RSE in 63% of the studies patients in a study carried out by by Synowiec et al[12], while this result was 72% in a study by Rosati et al[13]. The information regarding the therapeutic dosage or use of KE for the management of SE is scarce. Doses as high as 10mg/kg/hour have been used in various studies. The duration of the treatment should be seven days but most studies have shown that patients start showing response with 48 to 72 hours. In our study group seizure activity was terminated within 24 hours of the start of ketamine infusion. At present anesthetic agents are mostly used to terminate RSE. A systematic review by Claassen et al has shown the relative efficacy of pentobarbital, propofol and midazolam to be 42%, 66% and 60% respectively in terminating RSE[14] and these values are comparable to the efficacy of KE proven in our case series for the same purpose. Anesthetic agents carry a risk of high morbidity and mortality as compared to KE. KE therapy for RSE provides some added benefits. First of all ,there is upregulation of NMDA receptors during status epilepticus unlike GABA receptors. Secondly, it is thought that KE and other NMDA antagonists provide some neuroprotection even afrer SE. Thirdly, this drug is readily available and cheap. 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. Finally, the side effect profile in the neurological population, as documented in the literature to date, is low despite some initial concerns about potential neurotoxicity[15]. When dissecting the results etiology wise, KE was most effective in RSE of unknown etiliogy (81.8%, n=9/11) while it was least effective in RSE associated with remote symptomatic epilepsy (50%, n=1/3) in our study group. Further studies comparing effectiveness of KE and other anesthetic agents in patients with RSE secondary to various etiologies are required to as certain which drug to be used in which specific clinical condition.

We found that KE was generally safe in our patients as in only one patient (5%, n=1) ketamine had to be stopped due to intolerable side effects. The incidence of side effects was similar to other case series[16]. It was also found that mortality was lower (11% versus 36%) in patients in whom side effects did not occur.

The limitations of our study include small sample size, no randomization subject hetero-geneity, variability in timing and dose, and other confounding factors, for example, further co-administration of other drugs and lack of a control group for comparison. But at the same

time, it was a prospective study and KE was used prior to use of any other anesthetic agent if needed at all. Most of the other studies documenting KE efficacy in terminating RSE are retrospective (Gaspard et al, Synoweic et al, Rosati et al)[9,12,13]. KE was added in a fixed loading dose and continuous infusion and its efficacy was analyzed. The study results are consistent with other animal and retrospective human case series that ketamine is a potentially useful, safe and effective agent for termination of RSE.

CONCLUSION

In this small, open-label, unblinded study KE appears effective and safe in treating RSE in adults. Larger, randomized studies will help to confirm data emerging from this preliminary study.

CONFLICT OF INTEREST

This study has no conflict of interest to declare by any author.

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