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Review

Ketamine for the treatment of refractory status epilepticus

Yao Fang, Xuefeng Wang *

Department of Neurology, the First Affiliated Hospital of Chongqing Medical University, Chongqing 400016, China

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ABSTRACT

Status epilepticus (SE) is an acute and severe illness of the central nervous system, and prolonged SE can lead to brain damage and even death. Ketamine is a noncompetitive antagonist of glutamatergic *N*-methyl-D-aspartate (NMDA) receptors. During prolonged seizures, the numbers and activities of GABA receptors gradually decrease; thus, the commonly used first-line and second-line antiepileptic drugs gradually fail. Simultaneously, the numbers and activities of glutamatergic NMDA receptors increase, often causing refractory status epilepticus (RSE) and thus providing the possibility of the use of ketamine to treat RSE. To improve the prognosis of SE, we present a narrative review of ketamine for the treatment of RSE in the extant literature. We draw the conclusion that ketamine appears to be effective and relatively safe for the control of multidrug-resistant RSE in children and adults.

1. Introduction

Refractory status epilepticus (RSE) refers to status epilepticus (SE) that cannot be resolved in terms of clinical manifestations or epileptiform discharges following the rational administration of anticonvulsants including a benzodiazepine [1]. Super-refractory status epilepticus (super-RSE) refers to drug-resistant status epilepticus that persists or recurs following the continuous administration of intravenous anesthetics for more than 24 h [2], and the primary etiologies of super-RSE are brain insults, such as intracranial infection, brain trauma or stroke [2,3]. SE is an acute and severe illness of the central nervous system. When the seizure duration exceeds 30 min, the mortality rate is 19% [4]. Among RSE patients, the mortality rate is as high as 23–61% [5], and approximately 90% of RSE survivors ultimately relapse [4,6,7]. Ketamine could play an important role in the treatment of RSE by altering glutamate metabolism, particularly in patients who exhibit a poor response to benzodiazepines.

2. Background

Ketamine was developed by the Parke-Davis (USA) pharmaceutical company in 1962. Three years later, McCarthy et al. [8] found the first evidence that ketamine exerts an anticonvulsant effect in epilepsy animal models that were electrically or chemically created. These results were soon confirmed in patients [9], raising the possibility of treating SE using ketamine, although this possibility was soon questioned. The experiments by Kayama and Iwama [10] using cat models revealed that ketamine could induce epileptic changes, based on EEG recordings. However, a similar study of human volunteers conducted by Corssen et al. [11] rejected this conclusion. These authors found that ketamine did not cause epileptiform discharges in epilepsy patients or in normal subjects and that no evidence was available to support the notion that ketamine could induce or exacerbate convulsions, in contrast with the conclusions of Kayama [12,13].

In recent years, many researchers have reported that, during prolonged seizures, the number of activated GABA-A receptors on the postsynaptic membrane gradually decreases, whereas the number of inactive GABA-A receptors increases [14,15]. These changes cause a significant reduction in the efficacy of antiepileptic drugs (AEDs) that target the GABAergic system, such as diazepam, clonazepam, valproic acid, midazolam, propofol, and phenobarbital. Increased doses of AEDs might restore their efficacy, but the side effects of AEDs on cardiopulmonary function are simultaneously significantly increased, thus limiting the clinical applications of such increased doses. However, a study by Dingledine et al. [16] reported that the number and activities of glutamate-sensitive *N*-methyl-D-aspartate (NMDA) receptors significantly increased when the activity of GABA receptors decreased. Subsequently, this process induced continuously amplified neuronal hyperexcitability, leading to the development of RSE. Ketamine is a noncompetitive NMDA receptor antagonist [16] that might play a role in treating SE by blocking NMDA receptor-mediated glutamatergic

* Corresponding author. Tel.: +86 136 2835 9876; fax: +86 023 8901 2878.
E-mail address: xfyp@163.com (X. Wang).

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neurotransmission [17,18]. Moreover, by blocking glutamate-mediated NMDA receptor-induced neurotoxicity, ketamine also exerts neuroprotection [19–21]. Therefore, ketamine has been proposed as a new therapeutic agent for the treatment of SE [22–24].

3. Ketamine for the treatment of RSE

3.1. Clinical practice

Gaspard et al. [25] retrospectively analyzed the results of intravenous ketamine treatment of RSE. This study included 58 RSE patients treated with ketamine intravenously from 1999 to 2012, among whom 46 patients were adults, and 12 patients were children. These patients experienced a total of 60 episodes of RSE. The results indicated that, among the 57% (34/60) of cases in which the seizures ultimately resolved, approximately 32% (19/60) of the seizures were halted due to the effects of ketamine, and approximately 13% (8/60) of the cases of RSE were controlled during ketamine use. Similarly, a prospective study by Rosati et al. [26] also demonstrated that ketamine was relatively effective and safe for the treatment of RSE. This study included 9 RSE children who received intravenous ketamine between 2009 and 2011. In 8 patients, seizures had persisted for more than 1 day prior to ketamine selection. Finally, 6 patients who experienced RSE resolution were thought to be associated with ketamine administration, 2 patients were cured surgically, and no serious adverse reactions were recorded in all of the patients. In 2003, Mewasingh et al. [27] reported 6 cases of the use of oral ketamine to treat children (4–7 years old) with nonconvulsive RSE (NCSE), including Lennox–Gastaut syndrome, pseudo-Lennox syndrome, progressive myoclonic epilepsy and myoclonic-astatic epilepsy. All of the seizures remained prolonged despite the use of many anticonvulsants, and the median duration of these seizures was 4.4 weeks (range 2–10 weeks). Thus, these authors decided to use oral ketamine to treat RSE; fortunately, all of the patients experienced resolution within 24–48 h after the initiation of ketamine, resulting in a clear reduction in epileptiform discharges on EEG and improvement of the mental state of the patients. Although one of the children experienced a relapse a few months later, the continued use of ketamine remained effective, and no apparent side effects were recorded during ketamine treatment. Herein, we have summarized the available studies on ketamine for the treatment of RSE, which are presented in Tables 1 and 2. Collectively, these results indicate that ketamine is primarily suitable for the treatment of RSE and super-RSE during prolonged seizures, which is also supported by the conclusions of an animal

Table 1
Demographics and clinical data of ketamine treatment in RSE.

Year	Number of patients	Age (Y)/sex	History of epilepsy	Study type	Etiology of RSE	SE type	SE duration prior to KET	Medications prior to KET	References
2014	1	Newborn F	No	Case report	Brain malformation	GTCSE	About 9d	5 (PB, MDZ, LEV, PHT, PRO)	[29]
2013	58	24 (0.6–74) Unknown	Yes (9); unknown (49)	Retrospective study	Unknown (34); acute symptomatic (20); remote symptomatic (6)	GCSE (14); NCSE (42); FCSE (4)	9d (0–122d)	4.5 (1–10; unknown)	[25]
2013	11	52 (22–82) F (4); M (7)	Yes (6); no (5)	Retrospective study	Low AED levels (3); CNS infection (2); systemic infection (3); sepsis (2); metabolic disturbance (1)	GTCSE (6); NCSE (5)	5d (1–11d)	3–8 (DZP, LZP, VPA, LEV, TPM, CBZ, MDZ, PB, PHT, GBP, PRO)	[30]
2013	2	66; 57 F (1); M (1)	No	Case report	Elective aneurysm clipping	GTCSE (1); NCSE (1)	18d and 4d	8 (PHT, MDZ, PRO, LEV, TPM, PB, VPA, CLB) 5 (PHT, MDZ, PRO, VPA, LEV)	[31]
2013	1	27 F	No	Case report	Viral encephalitis	GTCSE	Unknown	9 (LZP, LEV, MDZ, PHT, LCM, PRO, TPM, PB, VPA)	[32]
2012	9	5.2 (1.3–10.4) F (5); M (4)	Yes (7); no (2)	Prospective study	Unknown (5); malformative (2); Rett syndrome (1); MELAS (1)	GCSE (3); focal (1); focal ± SG (5)	6d (5 h–26d)	5 (4–7; MDZ, TPM, CBZ, LEV, THP, PRO, VPA, PHT, PB, CZP, ETM, NZP, RUF)	[26]
2012	1	60 M	Yes	Case report	Unknown	NCSE	Within hours	4 (PHT, MDZ, PRO, LEV)	[33]
2011	1	76 F	Yes	Case report	Systemic infection; low AED levels	NCSE	9d	10 (VPA, MDZ, LEV, PHT, PRO, PB, LTG, CBZ, RGT, TPM)	[34]
2010	1	26 M	No	Case report	Unknown	GTCSE; NCSE	58d	8 (DZP, VPA, MDZ, LEV, PHT, TPM, PRO, THP)	[35]
2008	1	22 F	Yes	Case report	Unknown	GCSE	13d	5 (LZP, PHT, THP, LEV, PRO)	[36]
2005	1	15 M	No	Case report	Undefined, maybe encephalitis	Unknown	Unknown	4 (TPM, MDZ, PRO, PB)	[37]
2003	1	44 M	Yes	Case report	Neurosyphilis	GTCSE; NCSE	5d	5 (LZP, PHT, LTG, VPA, PRO)	[38]
2003	5	4 (4–7) F (3); M (2)	Yes (5)	Prospective study	Epilepsy syndrome	NCSE (5)	4.4w (2–10w)	0–3 (LZP, MDZ, prednisolone)	[27]
1998	1	13 F	No	Case report	Unknown	GTCSE	28d	8 (DZP, PHT, PB, LZP, LIDO, VPA, PRO, MDZ)	[39]
1996	1	Unknown M	Yes	Retrospective study	Cortical dysplasia	NCSE	Unknown	Unknown	[40]

AED: antiepileptic drug; CBZ: carbamazepine; CLB: clobazam; CNS: central nervous system; CZP: clonazepam; d: days; DZP: diazepam; ETM: ethosuximide; F: female; FCSE: focal convulsive status epilepticus; GCSE: generalized convulsive status epilepticus; GTCSE: generalized tonic-clonic status epilepticus; GBP: gabapentin; h: hours; KET: ketamine; LCM: lacosamide; LEV: levetiracetam; LTG: lamotrigine; LZP: lorazepam; M: male; MDZ: midazolam; MELAS: mitochondrial encephalomyopathy, lactic acidosis, and stroke-like episodes; NCSE: nonconvulsivestatusepilepticus; NZP: nitrazepam; PB: phenobarbital; PGB: pregabalin; PHT: phenytoin; PRO: propofol; RGT: retigabine; RSE: refractory status epilepticus; RUF: rufinamide; SE: status epilepticus; SG: secondary generalization; TPM: topiramate; THP: thiopental; VPA: valproate; w: weeks; Y: years.

Table 2
Ketamine treatment regime and efficacy.

Year	Number of patients	Administration	Dosages			Duration of treatment	Onset time	Time from ketamine initiation to seizure cessation	Seizure response	Outcome	References
			Bolus	Infusion	Oral						
2014	1	Intravenous	2 bolus of 2 mg/kg	10–24 μg/kg/min	0	2d	Unknown	Unknown	15d without seizures	SE reappeared and died	[29]
2013	58	Intravenous	Median 1.5 mg/kg (max 5 mg/kg)	Median: 2.75 mg/kg/h (max 10 mg/kg/h)	0	6 h–27d	Unknown	Unknown	57% resolved	Good outcome (5%); mortality (45%)	[25]
2013	11	Intravenous	1–2 mg/kg	1.3 mg/kg/h (0.45–2.1 mg/kg/h)	0	9.8 (4–28d)	Unknown	9.8 (4–28d)	Completely resolved	Home/rehabilitation (5); need nursing (4); died (2)	[30]
2013	2	Intravenous	0	10–40 μg/kg/min	0	3d and 12d	Within several hours; Within 30 min	3d and 12d	Completely resolved	Rehabilitation (2)	[31]
2013	1	Intravenous	1.5 mg/kg	1.2–3.75 mg/kg/h	0	12d	Unknown	Within 3d	Completely resolved	Rehabilitation	[32]
2012	9	Intravenous	0.75 mg/kg	0.6–3.3 mg/kg/h	0	2d	Immediately	12 h	Completely resolved	Home	[26]
2012	1	Intravenous	2 bolus of 2–3 mg/kg every 5 min	36.5 μg/kg/min (10–60 μg/kg/min)	0	6d (3–17d)	Unknown	Unknown	Completely resolved in 6	Unknown	[33]
2011	1	Intravenous followed with oral	1.5 mg/kg	0.05–4 mg/kg/h	1500–2000 mg/d	Unknown	Unknown	Unknown	Completely resolved	Home	[34]
2010	1	Intravenous	0.5 mg/kg	0.38–1.5 mg/kg/h	0	7d	2d	5d	Completely resolved	Rehabilitation	[35]
2008	1	Intravenous	0.5 mg/kg	0.4–3.2 mg/kg/h	0	14d	Unknown	10d	Completely resolved	Comatose, tetraplegic	[36]
2005	1	Intravenous	Unknown	Unknown	Unknown	Unknown	Unknown	Unknown	Failure	Died	[37]
2003	1	Intravenous	2 mg/kg	2–7.5 mg/kg/h	0	5d	Unknown	2d	Completely resolved	Diffused cerebral atrophy	[38]
2003	5	Oral	0	0	1.5 mg/kg/d in two divided doses	5d	Unknown	Within 1–2d	Completely resolved	Good outcome (5)	[27]
1998	1	Intravenous	2 μg/kg	7.5 μg/kg/h	0	14d	90s	2d	Completely resolved	Short-term memory and cognitive deficits	[39]
1996	1	Intravenous	0	100 mg/h	0	Unknown	Unknown	Unknown	Failure	Controlled by sub-pial transection	[40]

d: day(s); h: hour(s); kg: kilogram; min: minutes; s: seconds; SE: status epilepticus; μg: microgram.

experiment [28]. These authors found that if ketamine treatment was initiated after 15 min of SE, none of the animals exhibited responses to ketamine (0/4); however, when ketamine was initiated after 1 h of seizures, the successful termination rate was 100% (4/4). Moreover, after a prolonged seizure duration, a corresponding increase in the dose of ketamine was found to be effective within a certain time period.

3.2. An evidence-based clinical study on the use of ketamine to treat RSE

In 2014, Zeiler et al. [41] published a systematic review of NMDA-receptor antagonists for the treatment of RSE. Twenty-three studies were ultimately included in this analysis, which included a total of 162 patients consisting of 110 adults (range 19–88 years old) and 52 children (range 2 months–18 years old). In all of these studies, ketamine was used to treat RSE. This study revealed that ketamine was effective for 56.5% (59/110) of the adults and 63.5% (33/52) of the children and that the rate of side effects related to ketamine administration was 1.8% (2/110) in the adults and 17.3% (9/52) in the children, supporting the use of ketamine for the treatment of RSE in children and adults and indicating that adverse reaction rates related to ketamine administration were relatively small. However, this review also has some limitations such as the retrospective heterogeneous nature of the data, the small sample sizes of the studies included, and the heterogeneity of the medications prior to ketamine treatment, the timing of ketamine use, and the dosage and duration of this drug. Thus, larger prospective studies are necessary to assess the efficacy and safety of ketamine treatment in RSE.

4. The possible antiepileptic and neuroprotective mechanisms of ketamine action

4.1. The possible mechanism of the effects of ketamine on SE

With decreased GABA-receptor activity, the expression of the NMDA receptor is up-regulated, and the activity of this receptor is also increased in late SE. The NMDA receptor is one of the main receptor subtypes that mediates glutamatergic neurotransmission, and it is also a nonspecific cation channel that contains the NMDA binding site and the phencyclidine (PCP) binding site [42]. When the cell is at rest, Mg^{2+}, located on the inner side of the channels, blocks the channels. When the cell membrane is depolarized, the combined actions of glutamate and glycine on the NMDA receptor remove the blocking effect of Mg^{2+}, and the activation of the receptor can induce influxes of calcium and sodium, which participate in the transmission of excitatory nerve impulses in different brain circuits [16]. However, ketamine, which is a noncompetitive antagonist of the NMDA receptor, can block the flow of Ca^{2+} and Na^{+} by combining with the PCP site inside of the ion channel of the NMDA receptor and can thereby reduce epileptiform burst discharges and after-potentials, thus inhibiting the conduction of excitation and playing an anticonvulsive role [18].

4.2. The neuroprotective effects of ketamine

With prolonged SE, cell depolarization also continues, leading to the excessive release of excitatory neurotransmitters that can bind to a variety of receptors to produce neurotoxicity. Among these receptors, the NMDA receptor might play a critical role in this effect [43–47]. do Nascimento et al. [48] detected hippocampal neuronal damage in rats in which SE had been induced by pilocarpine. Using Fluoro-Jade (FJB) and cresyl violet staining, these authors detected multiple sites of neuronal damage 3 h, 6 h, 12 h, 24 h, 1 week, and 3 weeks after prolonged SE. These sites of damage were primarily located in the hippocampal dentate gyrus, the CA1 zone, and the CA3 zone. Moreover, the neuronal damage was most extensive in the dentate hilus after 3 and 12 h of seizures ($P < 0.05$). However, one week after the seizures, the greatest neuronal damage was located in the pyramidal cell layer of the CA1 and CA3 regions in the hippocampus ($P < 0.05$), and the most serious neurotoxicity was observed in the hippocampal CA1 pyramidal cell layer ($P < 0.05$). The NMDA receptor antagonist ketamine not only blocks the influx of Ca^{2+} but also exerts anti-inflammatory and antioxidant effects [49,50]. Therefore, ketamine exerts protective effects in the central nervous system. Fujikawa [51] used pilocarpine to induce epilepsy in a rat model and then administered 100 mg/kg ketamine or saline to the rats via intraperitoneal injection after 10 min of seizures. Three hours later, the seizures were terminated with intraperitoneal injections of diazepam and phenobarbital. After 24 h, these authors performed perfusion fixation to obtain slices of the rat brains, which were observed under a microscope. They found that, in the 5 rats that had been injected with saline, neuronal damage was observed in 24 of 25 brain regions; however, in the 7 rats that received ketamine treatment, the drug was found to exert neuroprotective effects in 22 of the 24 damaged brain regions. Regardless of whether the seizures were ultimately terminated, this neuroprotection remained present and was beneficial to the recovery from SE.

5. Onset time

Ketamine displays relatively high fat solubility and a low plasma protein binding rate, causing it rapidly penetrate the blood–brain barrier; thus, ketamine exhibits the property of rapid onset. It has been reported that, when ketamine is administered intravenously, the interval to the maximum plasma concentration (T_{max}) is from 1 to 5 min, and when ketamine is administered orally, the T_{max} is from 15 to 30 min [52]. As observed by Kramer [33], when a bolus of 50 mg of ketamine was intravenously administered, followed by infusion at an initial rate of 0.6 mg/kg/h, reduced seizure frequency, shortened seizure duration, and decreased epileptiform discharge amplitude were immediately observed, indicating that ketamine acts rapidly in the treatment of RSE. This conclusion has been supported by other studies [39,53]. Additionally, Sheth and Gidal [39] noted that the onset time of intravenous ketamine was within 90 s after initiation. However, in the majority of cases, seizures are often completely terminated within 24 h when ketamine is selected for the treatment of SE [25]. When ketamine is administered orally, the interval to complete seizure control is within 24–48 h [27].

6. Dosage

Currently, the administration of ketamine for the treatment of RSE involves intravenous and oral routes. When ketamine is selected for RSE treatment following prolonged SE, it maybe typically suitable after 5–6 anticonvulsants have been found to be ineffective. This treatment choice is summarized from previous successful reports [25,26,29], and the rationale for its use is based on prolonged seizure duration, decreased numbers of active GABA receptors, gradual elevation of NMDA receptor activity, and increased numbers of NMDA receptors [14–16,54,55].

6.1. Intravenous administration

(1) Intravenous bolus followed by continuous infusion: when ketamine is used for adult RSE, an average loading dose of

1.5 mg/kg, followed by an average infusion rate of 2.75 mg/kg/h for 4 days (0–24 days) is recommended [25]. An analysis by Gaspard et al. [25] revealed that the maximum loading dose of ketamine is 5 mg/kg and that the maximum infusion rate is 10 mg/kg/h. Moreover, Synowiec et al. [30] found that a bolus dose of 1–2 mg/kg, followed by maintenance at an infusion rate of 1.3 mg/kg/h (range 0.45–2.1 mg/kg/h) for 9.8 days (range 4–28 days), resulted in a successful seizure control rate of 100% (11/11). When ketamine is administered to children, we recommend a 2–3 mg/kg bolus of ketamine every 5 min for a total of 2 administrations, followed by maintenance at a rate of 40 μg/kg/min (range 10–60 μg/kg/min) for 6.7 days (range 3–17 days) [26]. (2) Intravenous infusion: Zelier et al. [31] performed continuous infusion of ketamine at 10–40 μg/kg/min for the treatment of RSE, and the seizures in all of the patients were ultimately effectively controlled (2/2). In a report by Gosselin-Lefebvre et al. [56], ketamine was initiated in 9 SE patients when 8 AEDs had failed, and the seizures had persisted for 12 days. The average rate of ketamine infusion was 5 mg/kg/h (range 2–15 mg/kg/h). Ultimately, the seizures were completely halted in 4 patients (4/9), partially controlled in 3 patients (3/9), and not controlled in only 2 patients (2/9). Finally, the recommended dosage for children is 32.5 μg/kg/min (range 10–60 μg/kg/min) when intravenous infusion of ketamine alone is selected [57].

6.2. Oral administration

The use of oral ketamine to treat RSE has only been reported in NCSE. The recommended dosage of ketamine is 1500–2000 mg/d for adults [34] and 1.5 mg/kg/d, administered as two separate doses, for children [27].

The usage of ketamine for the treatment of RSE is summarized in Table 3.

7. Adverse reactions and precautions for ketamine use

Zeiler et al. [41] performed a systematic review, which indicated that the adverse reactions related to ketamine treatment for RSE were rare. However, due to the lack of controlled studies related to this topic, concern remains warranted, primarily regarding psychiatric symptoms during anesthesia recovery, increased intracranial pressure (ICP), increased secretion of saliva, increased intraocular pressure, and arrhythmia. Details regarding the adverse reactions and precautions for ketamine use are described as follows.

7.1. Psychiatric symptoms

The psychiatric symptoms caused by treatment of RSE with ketamine are primarily related to hallucinations, delirium, a floating sensation, dreams, and blurred vision [58]. The incidences of these symptoms are 5–30%. Children are at the lowest risk for psychiatric symptoms, which are more likely to occur in patients over 16 years old, in female patients, or when the administration rate or dosage is too high [58]. A quiet and relaxing environment can help to reduce the incidences of these side effects [59]. Additionally, prophylactic administration of 3.75–7.5 mg of midazolam could reduce the probability and severity of adverse reactions [59].

7.2. Increased ICP

As early as 40 years ago, there were reports that ketamine improved the cerebral metabolic rate and increased cerebral blood flow, thereby increasing ICP [60]. However, due to the developments of related studies, researchers have proposed new hypotheses regarding the effects of ketamine on ICP, finding that, when patients are breathing spontaneously, ketamine causes intracranial hypertension that is primarily associated with increased $PaCO_2$ in the arterial blood; however, when patients are sedated and mechanically ventilated, the effects of ketamine on ICP are, in fact, very small [59]. A systematic evaluation, published in 2014, showed that, when ketamine was used for nontraumatic neurological diseases, it did not increase ICP, and in some cases, ketamine might even reduce ICP [61]. Gaspard et al. [25] studied 58 patients treated with ketamine and observed only 2 cases of mild ICP elevation. Actually, prior to the initiation of ketamine, these 2 patients had suffered from brain edema secondary to anoxic brain injury.

7.3. Increased secretion of saliva

Ketamine can induce the secretion of saliva, accompanied by the hypersecretion of bronchial mucus, which can lead to transient inhibition of the respiratory system or apnea. To prevent this adverse effect, anticholinergic drugs, such as scopolamine or atropine, can be prophylactically administered during the clinical application of ketamine treatment [52].

7.4. Increased intraocular pressure

The effects of ketamine on intraocular pressure remain controversial [62]. Some authors believe that ketamine can cause an increase in intraocular pressure [63], whereas others have stated that it can reduce intraocular pressure [64] or that ketamine exerts no effect on intraocular pressure [65]. This discrepancy may be attributable to the many factors that can influence intraocular pressure, such as the aqueous humor circulation, extraocular muscle tension, choroidal blood flow, vitreous volume, etc. [50]. In fact, the influence of ketamine on intraocular pressure has been shown to be mild and even smaller than the effects of laryngoscopy [50]. Thus, when ketamine is used for RSE, it exerts little effect on intraocular pressure, and the combined use of benzodiazepines can alleviate this effect [62].

Table 3
Usage of ketamine for the treatment of RSE.

Administration	Indication	Contraindications [72]	Dosages		Onset time [52]
			Adults	Children (0–18 y)	
Oral	After 5–6 ADEs failed	Allergic Severe hypertension	1500–2000 mg/d [34]	1.5 mg/kg/d in two divided doses [27]	15–30 min
Bolus and infusion	After 5–6 ADEs failed	Allergic Severe hypertension	Bolus: 1–5 mg/kg Infusion: 0.45–10 mg/kg/h [25,30]	Bolus × 2: 2–3 mg/kg Infusion: 2.4 mg/kg/h (range 0.6–3.6 mg/kg/h) [26]	1–5 min
Infusion	After 5–6 ADEs failed	Allergic Severe hypertension	0.6–15 mg/kg/h [31,56]	1.95 mg/kg/h (range 0.6–3.6 mg/kg/h) [57]	1–5 min

7.5. Arrhythmia

The arrhythmias induced by ketamine are often tachyarrhythmias, which might occur because ketamine can excite the sympathetic nervous system and shorten atrial conduction [66,67]. Gaspard et al. [25] examined 58 RSE patients who received ketamine and found that only 3 patients exhibited arrhythmias. Two of these patients exhibited supraventricular tachycardia, and their symptoms were alleviated following the withdrawal of ketamine. The other patient exhibited atrial fibrillation that was relieved using amiodarone.

7.6. Neurotoxicity

The effects of ketamine on the human central nervous system remain controversial. In 1991, it was found that ketamine exerts toxic effects on some regions of the cerebral cortex in rats. Ketamine was found to be capable of causing regional neuronal vacuolation or even necrosis, and since this finding, clinicians have become more cautious regarding the selection of this drug. However, over the last 20 years, this conclusion has yet to be confirmed or generally accepted [68]. Most researchers believe that regular doses of ketamine cause only mild neurotoxicity, possibly because of the short half-life of this drug in the body and the low affinity of ketamine for NMDA receptors. Moreover, this neurotoxicity is likely limited to very young patients [69,70].

7.7. Precautions for ketamine use

Considering about the adverse reactions stated above, precautions should be considered during ketamine use. Due to the excitatory effects of ketamine on the central nervous system, the Food and Drug Administration (FDA) recommends that ketamine use be contraindicated in patients with severe hypertension and in patients who are allergic to ketamine. Patients with coronary heart disease, heart failure, glaucoma, atherosclerosis, pulmonary heart disease, pulmonary hypertension, severe intracranial hypertension, pregnancy, a history of mental illness, hyperthyroidism, tachyarrhythmia, adrenal pheochromocytoma, and alcoholism should receive ketamine with caution [71]. Additionally, the FDA has provided the following recommendations [71]: (1) slower infusion rates and gradual increases in the dosage should be considered because, when the ketamine administration rate or dosage is too high, psychiatric symptoms, as well as respiratory depression and apnea, are more likely to occur during recovery from anesthesia; (2) to reduce seizures and ketamine-induced respiratory depression, mechanical ventilation should be employed prior to ketamine initiation, and vital signs, such as breathing status and blood pressure, should be closely monitored; (3) computed tomography should be performed to exclude the presence of intracranial lesions that might cause intracranial hypertension before the selection of ketamine; (4) in the elderly, the minimum possible dose of ketamine should be selected; and (5) ketamine might increase skeletal muscle tension in some patients, which should be distinguished from tonic-clonic seizures.

8. Conclusions

Ketamine is a noncompetitive antagonist of glutamatergic NMDA receptors, and its anticonvulsant effects have previously been confirmed. Recent studies have found that, during prolonged seizures, the numbers and activities of GABA receptors gradually decrease; thus, the commonly used first-line and second-line AEDs gradually fail. Simultaneously, the numbers and activities of glutamatergic NMDA receptors increase, often causing RSE and thus providing the possibility of the use of ketamine to treat RSE. Additionally, ketamine exerts neuroprotective effects that could ameliorate RSE-induced neuronal damage. Therefore, in recent years, ketamine has become increasingly used in clinical practice.

We examined many clinical studies that have investigated the efficacy of ketamine in the treatment of RSE; these studies included multi-center, retrospective studies, prospective cohort studies and case reports. In addition, the results of an evidence-based clinical study, published in 2014, also suggested that ketamine might be of potential benefit, and it reported low adverse reaction rates in the treatment of RSE in children and adults. However, to the best of our knowledge, no controlled studies have been published that have examined the efficacy and safety of ketamine for the treatment of RSE, constituting a limitation of our review. However, it is not ethically permissible to establish randomized controlled trials in patients with RSE, due to the emergent nature and high mortality of this disease and the lack of effective drugs to treat RSE to use as a control. In addition, the unpredictable nature, low recruitment rates, and relatively low incidence rates of RSE have also resulted in a lack of large-sample-size studies. In addition, the first planned RCT focusing on the treatment of RSE was terminated due to insufficient recruitment [72]. Thus, it will be necessary to conduct robust prospective studies to investigate the regimens, efficacy, and safety of ketamine for the treatment of RSE.

Conflict of interest

All the authors declare that they have no conflict of interest.

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