Khaled Abdullah Alzahrani et al. Saudi J Er Med. 2023;4(1):060-072
https://doi.org/10.24911/SJEMed/72-1667716410

REVIEW ARTICLE

The efficacy and safety of ketamine in refractory and super-refractory status epilepticus: a systemic review

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ABSTRACT

Background: In published animal studies, N-methyl-D-aspartate antagonists such as ketamine (KET) have been reported to reduce Status epilepticus (SE) even after benzodiazepines had failed. In addition, there are studies on the human population that have reported on the use of KET to manage SE seizures. However, despite its history of use as an anesthetic, there are few published review studies on using KET in the treatment of refractory SE (RSE).

Objective: This research aims to determine whether KET is an effective treatment for RSE and super-refractory (SRSE) in both children and adult patients.

Methods: A systematic search was done on PubMed, EMBASE, Google Scholar, and Cochrane databases from inception until September 12, 2022. In addition, a search was also done for gray literature (ClinicalTrials.gov and World Health Organization International Clinical Trials Registry Platform).

Results: The initial search identified 164 articles and only 21 were included in this systematic review; 10 case reports, 9 case series, and 2 cohort studies. In total, the study population is 408. Regarding individual case reports, there were 56 cases, of which 52 were adults. In addition, there were 27 males, 26 females, and 3 unidentified (50).

Conclusion: The admission of KET as management for RSE and SRSE has effectively controlled and terminated SE seizures. KET presented to generally be safe, as there are a few reported adverse events. The mortality rates appeared to be high, but none of the studies reported any direct link between these adverse outcomes and using KET to manage SE.

Keywords: Ketamine, midazolam, status epilepticus, seizures, review, adult, pediatric, hemodynamics.

Introduction

Status epilepticus (SE) is a neurological emergency that must be treated immediately to avoid severe morbidity or fatality [1,2]. In 2012, the Neurocritical Care Society defined SE as a seizure lasting for 5 or more minutes; and characterized by continuous clinical and/or electrographic seizure activity, repeated seizures, or seizures with no intersegmental recovery [2-4]. SE can occur in people with epilepsy [5]. These data are seconded by a report by Stasiukynienė et al. [6], which reported that 25% of people who experienced SE had a history of epilepsy. SE can also be caused by underlying neurological disorders, including trauma, infections, and strokes [5-7].

Based on clinical features, SE can be categorized into convulsive (CSE) and non-convulsive SE (NCSE) [7,8]. CSE is characterized by a consistent pattern of arm and leg contraction and extension [8]. NCSE is generally a long-lasting alteration in a person's state of awareness that is not accompanied by large-scale flexion and extension of the limbs [9]. Up to 25% of SE instances are non-convulsive [9]. There are two primary types: prolonged, complex

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Received: 06 November 2022 | **Accepted:** 02 December 2022

seizures, and absence seizures [9]. In complex partial SE, the seizure is often restricted to a small temporal lobe region [10]. It is sometimes called fugue status or psychomotor status [10]. On the other hand, the absence of SE is characterized by a seizure that affects the entire brain [11,12]. To differentiate between the two situations, an electroencephalogram (EEG) is required [12]. EEG is a test that monitors electrical activity in the brain using electrodes (small metal discs) affixed to the scalp [12,13]. Because brain cells are always alive and interacting via electrical impulses even when asleep, the EEG can produce undulating lines representing brain activity [13].

SE can also be categorized as refractory (RSE) or super-refractory (SRSE). RSE is SE that persists even after therapy with benzodiazepines and at least one antiepileptic medication [14].SRSE is described as SE that persists or recurs 24 hours or more following anesthetic treatment, including incidents in which SE resurfaces upon relaxation or discontinuation of anesthesia [15]. Currently, there is no factual data or consensus about the appropriate RSE therapy [15-17]. Coma induction with high-dose midazolam (MDZ) or conventional anesthetics such as thiopental, pentobarbital, or propofol is commonly used to treat RSE and SRSE [17-19].

Most seizures cease spontaneously after a few minutes [20], probably due to y-aminobutyric acid-mediated recurring inhibition in response to seizures. When seizures persist, however, inhibitory y-aminobutyric acid receptors are internalized in clathrin-coated vesicles [21]. The internalization of -aminobutyric acid receptors may explain the clinical observation that benzodiazepines, which function via -aminobutyric acid pathways, are less efficacious as seizure durations grow [21,22]. This finding may imply a role for N-methyl-d-aspartate-(NMDA) modulating drugs such as ketamine (KET). Apart from general benzodiazepines and KET, other commonly used treatments are pentobarbital, phenobarbital corticosteroids, MDZ, propofol, inhaled anesthetics, topiramate, levetiracetam, the KET diet, pyridoxine, electroconvulsive therapy, and valproic acid [17].

KET is a non-competitive NMDA glutamate receptor antagonist that may be therapeutic in the later phases of RSE due to its independence from γ-aminobutyric acid-related processes [22]. Mewasingh et al. [23] conducted a study including five children between 4 and 7 years with severe epilepsy and refractory NCSE lasting for a mean duration of 4.4 weeks. The population was treated using oral KET, and all patients responded within 48 hours, as measured by reduced seizures on the EEG and improved mental status. A few months later, only one kid experienced a relapse of NCSE, which was again effectively treated with KET. No adverse events were reported in the study [23]. In a separate case report presented by Sheth and Gidal [24], clinical and electrographic seizures that had persisted for 4 weeks in a 13-year-old girl with RSE ceased within 90 seconds of an IV KET. For the next 2 weeks, she was treated with IV KET (maximum dose of 7.5 g/kg/hour), which reduced the frequency of her seizures to a few per day [24].

Some studies have reported increased intracranial pressure (ICP) after KET administration for lumbar-puncture sedation [25]. However, recent literature analysis hasn't discovered any evidence to show that KET directly impacts increased ICP [17]. In fact, KET has been linked to enhanced brain perfusion [26]. KET sympathomimetic characteristics may enhance cerebral blood flow by boosting blood pressure, in contrast to most drugs used to treat RSE, which drops blood pressure [26]. This concern was also raised by Leitinger et al. [27] and Holtkamp and Meierkord [28] in the use of traditional aesthetics in the treatment of less severe SE with potential impairment of consciousness [8].

According to Rosati et al. [8], KET is thus to be considered in the treatment of RSE, particularly in the latter phases when medicines rely on -aminobutyric acid augmentation are ineffective [8].

Despite the long-standing use of KET as an anesthetic, there is a little published experience in the treatment of RSE with KET, based on its promising efficacy and good safety profile, KE may be considered the anesthetic agent of choice in specific situations and as an out-of-hospital treatment option for SE.

KET is currently administered in patients with RSE only when conventional anesthetics have failed; however, based on its potential efficacy and good safety profile, many hospital policies recommend an earlier administration. Here, we performed a systematic review of the literature on the efficacy and safety of KE in treating RSE in pediatric and adult populations.

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Materials and Methods

Justification for research

Internalization of γ-aminobutyric acid type-A receptors to the synapse and enhanced expression of NMDA receptor to the synapse are essential factors of seizure persistence in SE [29]. As time passes, aminobutyric acid type A-mediated inhibition becomes less efficient, and glutamate's excitatory activities grow more potent. Therefore, coma induction with high-dose MDZ or conventional anesthetics such as thiopental, pentobarbital, or propofol is commonly used to treat refractory CSE. However, there are worries about using traditional aesthetics in less severe types of NCSE without consciousness loss [8].

Study objectives and research question

In published animal studies, NMDA blockers such as KET were successful in reducing SE even after

benzodiazepines failed [30,31]. According to Borris et al. [32], animal studies showed a late (1 hour) but not early (15 minutes) effectiveness of KET, suggesting that it may be ineffective before receptor modifications occur [32]. Another merit is that KET may be neuroprotective by lowering excite-toxic damage mediated by NMDA receptors [33]. Despite its long history of usage as an anesthetic, there have been few published review studies on the treatment of RSE with KET. This systematic review examines all clinical research on KET in treating SE.

Research question

Is KET effective and safe in treating RSE and SRSE in pediatric and adult populations?

This research question was developed and presented using the PICO format.

Population	Pediatric and adult populations.
Intervention	KET
Comparison	Alone or with other agents
Outcome	Control of seizure activity after KET treatment was the primary outcome measure, and it was seen clinically or verified by EEG. This control was further defined as complete control, which meant that all patients experienced total remission of seizures indefinitely; moderate control, mild control, poor control, and failed control were the other categories.

Search methodology

To further understand the effects of KET in treating RSE and SRSE, a comprehensive web-based advanced literature search was conducted using the NHS Library Evidence tool. The protocol for this systematic review was regularly registered on International Platform of Registered Systematic Review and Meta-analysis Protocols (INPLASY), identified record number INPLASY2022110011. This systematic review was carried out following guidelines outlined in the Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA) statement [34].

Information sources

A systematic search was done on PubMed, EMBASE, Google Scholar, Cochrane databases, and gray literature (ClinicalTrials.gov and World Health Organization International Clinical Trials Registry Platform); from inception until September 12, 2022, to identify topic-relevant articles. The search was structured by combining the main keywords of the topic: "ketamine: AND "Refractory and Super Refractory Status Epilepticus."

Inclusion and exclusion criteria

The eligibility criteria were developed using PICO guidelines (Table 1).

Data selection process

All identified articles were evaluated in two stages. Initially, two reviewers independently assessed all returned papers' titles, abstracts, and full texts to determine whether they fulfilled the inclusion criteria. Second, differences of opinion between the two reviewers were solved through scientific-based discussion.

Study quality assessment

Case reports and case series will be evaluated by the CARE criteria. The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement will be used to evaluate the study quality of Cohort studies. We will consider studies with a complete STROBE checklist for cohort studies to be high quality and include them in our review.

Data extraction

Two reviewers independently extracted data from the selected articles and stored it in an electronic database. The following data were extracted: study type and design, patient demographics, number of patients, type of SE (CSE, NCSE and subtle SE, focal and generalized SE), etiology of SE, dose, timing, duration, and route of KE administration, prior and concomitant therapies, outcome defined as electrographic SE control and adverse events. Considering the different etiologies of SE across ages, data on pediatric and adult populations will be analyzed separately.

Data synthesis

A systematic assessment of the available evidence was conducted following the GRADE methodology and the PRISMA checklist (Figure 1). A meta-analysis was found to not be due to a lack of prospective randomized trials. This article uses qualitative analysis, which is thematic, narrative, and textual, to assess, synthesize, and summarize the body of evidence included herein. Qualitative analysis was aimed to:

Briefly summarize the included research, highlighting their major characteristics and key findings.

Analyze the relationships between studies, exploring patterns and investigating heterogeneity.

Table 1. *Eligibility criteria.*

PICO	Inclusion criteria	Exclusion criteria
Population	Pediatric and adult populations.	Animal studies
Intervention	KET	Non-KET
Comparison	With or without other agents	
Outcomes	The main outcome is reduced or eliminated seizure activity following KET therapy, as observed clinically or confirmed by an EEG.	Any articles that don't have our outcome, any preclinical studies, editorials, letters, and non-English publications.

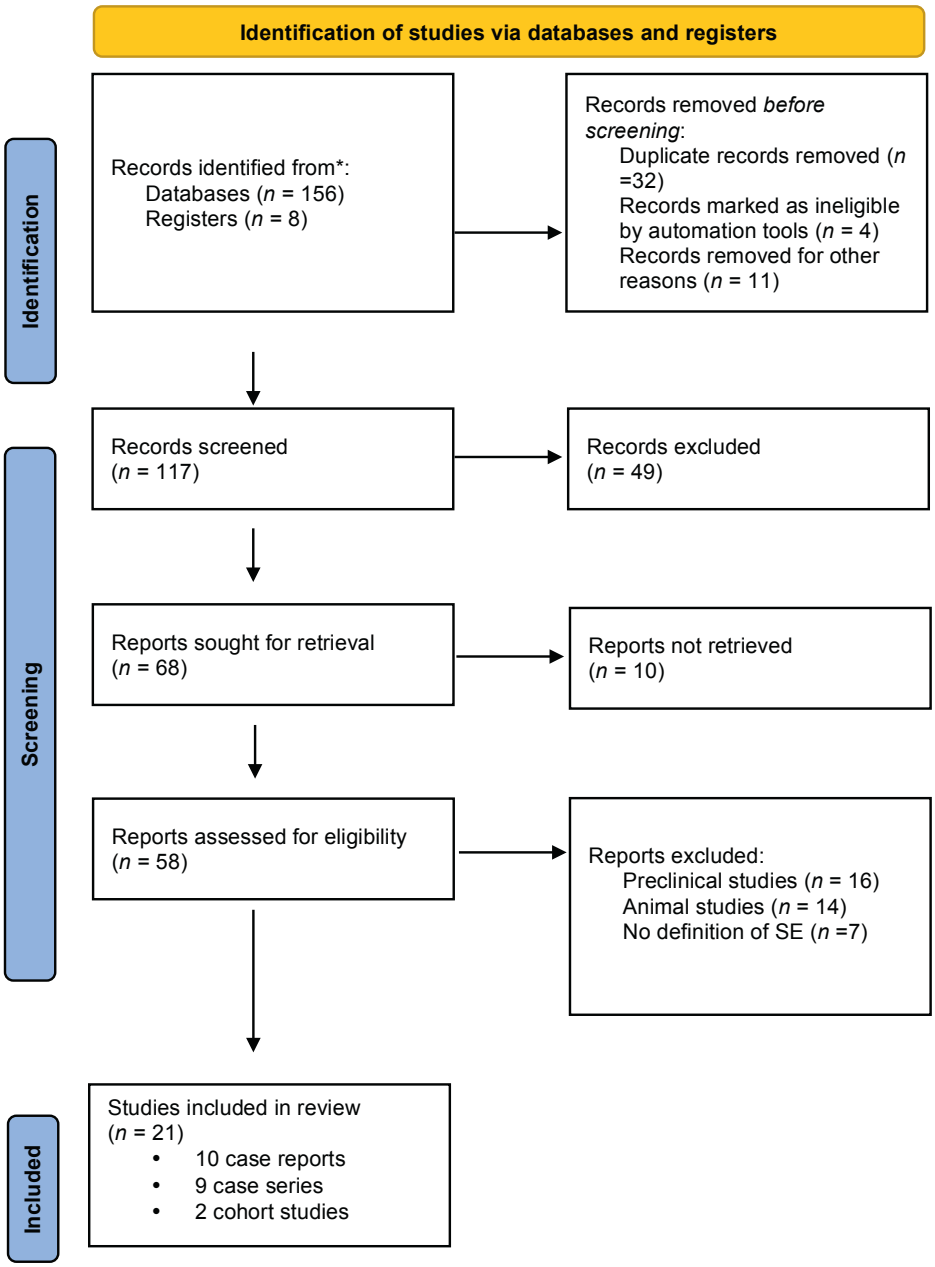

Figure 1. *PRISMA 2020 flow diagram for new systematic reviews, which included searches of databases and registers only.*

Within the context of the PICO structure, discuss how the body of evidence can be applied to the issue being asked by the review.

Explain the meta-analysis, if one was performed, as well as an interpretation and analysis of the results it obtained.

We are giving a critical appraisal and evaluating the overall quality of the evidence, including a meta-analysis of the study's risk of bias.

Consider any gaps in the research, such as insufficiently investigated patient populations or those for whose findings vary.

Compare the review's findings with current conventional wisdom when appropriate.

Results

The initial article search identified 164 articles. Thirty-two duplicates were removed, and 15 articles were removed because of irrelevancy, 4 of them by automation tools. The remaining 117 articles were reviewed, and 49 of them were excluded since they did not satisfy the inclusion criteria. Sixty-eight study reports were sought for retrieval, but only 58 were available for full-text article review. Among the 58 full-text articles, 16 were excluded since they were preclinical studies, 14 because they were animal studies, and 7 because they did not clearly define SE. This study selection process is graphically presented below as a flowchart. This review article includes 21 studies, 10 case reports, 9 case series, and 2 cohort studies. Each case

report had one case except for Zeiler et al. [36], Shrestha et al. [38], and McGinn et al. [39], which reported two cases each. Among the case series and cohort studies, the lowest population was 3 in DeVine et al. [50], and the highest was 69 in Jacobwitz et al. [54]. In total, the review population is 408. Regarding individual case reports, there are 56 cases, and 52 are adults (Table 3). There are 27 males, 26 females, and 3 unidentified [50].

Results of quality assessment

Case reports and case series were assessed using the CARE guidelines, and fulfillment of a checklist item was awarded 1 point. The possible maximum score was 13 points, Cohort studies were assessed using the STROBE guidelines; the possible maximum score was 22 (Table 2).

For CARE criteria, low quality (0-4), medium quality (4-8), high quality (9-13); for STROBE criteria, low quality (0-7), medium quality (8-15), high quality (16-22).

Data extraction results

Data were extracted independently from the selected articles by two reviewers and stored in an electronic database. Data fields for cases reports included study design, age, etiology, previous treatment/anesthetic, mean RSE duration before KE infusion (range), mean KE dosage (mg/kg/hour), mean duration of receiving KE, co-therapy treatments, clinical response, EEG before KET, EEG after KET, clinical outcome, and adverse events.

Data fields for case series and cohort studies included authors and year, patients number, mean age, sex (% F), RSE type, etiology, previous treatment/anesthesia, mean RSE duration prior to KE infusion (range), mean KE dosage (mg/kg/hour), mean duration of receiving KE, and Co therapy treatments. The clinical outcome for all case series and cohort studies are summarized in Table 5. The clinical outcome for all case series and cohort studies are summarized in Table 5.

Discussion

Early treatment

The number, types, duration of infusion, and dosage of anti-epileptic drug (AEDs) and anesthesia varied from one study to another. The most applied first-hand anesthesia and AEDs are phenytoin, propofol, MDZ, clobazam, Keppra, levetiracetam, lacosamide, topiramate, phenobarbital, pentobarbital, and valproic acid/valproate.

KET treatment

In most case reports and case series, KET was administered after other drugs and anesthetics had failed to eliminate seizure activity. Like other treatments, the duration and dosage of administered KET varied broadly. The mean dose per study ranged from 35 mg bolus [38] to 50 mg bolus [35], and Intravenous (IV) rate from 0.07 [42] to 5 mg/kg/hour [46]. The duration of Ketamine (KE) infusion ranged from 24 hours [38,39,50,52] to

Table 2. *Study quality.*

Study	Study design	Quality score	Comment
Case reports			
Kramer [35]	Prospective	10	High quality
Zeiler et al. [36]	Retrospective	10	High quality
Esaian et al. [37]	Prospective	10	High quality
Shrestha et al. [38]	Prospective	9	High quality
McGinn et al. [39]	Prospective	10	High quality
Dillien et al. [40]	Prospective	10	High quality
Talahma et al. [41]	Prospective	10	High quality
Koffman et al. [42]	Retrospective	11	High quality
Vallecoccia et al. [43]	Prospective	11	High quality
Yousif et al. [44]	Prospective	12	High quality
Case series			
Synowiec et al. [31]	Retrospective	10	High quality
Gaspard et al. [45]	Retrospective multicenter	10	High quality
Basha et al. [46]	Retrospective	10	High quality
Sabharwal et al. [47]	Retrospective	10	High quality
Höfler et al. [48]	Retrospective	9	High quality
Alkhachroum et al. [49]	Retrospective	9	High quality
DeVine et al. [50]	Retrospective	10	High quality
Dericioglu et al. [51]	Retrospective	10	High quality
Caranzano et al. [52]	Retrospective	8	Medium quality
Cohort studies			
Keros et al. [53]	Retrospective	21/22	High quality
Jacobwitz et al. [54]	Retrospective	20/22	High quality

Table 3. *Presentation of adult and pediatric cases: case reports.*

Authors and year	Age and sex		RSE type	Etiology	Previous treatment/ anesthetic	Mean RSE duration before KE infusion (range)	Mean KE dosage (mg/ kg/hour)	Mean duration of receiving KE	Co-therapy treatments	Clinical response	EEG before KET	EEG after KET	Clinical outcome	Adverse events
Adult														
Kramer [35]	60	M	NCSE	Cerebral palsy, epilepsy	MDZ, PRO	Unclear	50 mg bolus+ max 220 mg/ hour (3.3 mg/ kg/hour)	2 days	MDZ, PRO	Yes (reduction in the prevalence, duration, and amplitude of seizures)	NR	DLA	General improvement	None
Zeiler et al. [36]	66	F	NCSE	Unidentified	PRO, MDZ, Keppra, PB	12 days	Started at 10 mg/kg/minute, maximum 20 mg/kg/minute	>3 days	Topiramate at 100 mg twice daily	Yes (burst suppression on EEG)	NR	NR	General improvement	None
	57	M	NCSE	NR	PHT, MDZ, PRO, PRO	4 days	40 mg/kg/ minute	5 days	MDZ, PRO	Yes (burst suppression within 30 minute)	NR	Diffuse sharp spike-wave activity	No EEG evidence of seizures 7 days after weaning of KET	None
Esaian et al. [37]	27	F	Subtle SE	NR	PHT, PRO infusion, MDZ, PB, LEV	Unclear (14 days)	1.2 mg/kg/hour	12 days	MDZ, N acetylcysteine (NAC) therapy, PHT, PRO, PB	Yes (decreased frequency of periodic epileptic discharges)	Reducing the frequency of generalized frequent epileptic discharges and multifocal discharges	Faster frequencies and no epileptiform discharges or seizures.	General improvement	None
Shrestha et al. [38]	23	F	CSE	Generalized seizure activity	LZP bolus, PHT, MDZ	36 hours	100 mg/hour	2 days	MDZ	Yes	NR	EEG showed no seizure activities	Improved general activity	None
	30	F	CSE	NR	MDZ bolus and PHT	24 hours	35 mg bolus followed by 70 mg/hour	24 hours	MDZ	Yes	NR	Decreased frequencies of convulsive seizures	Improved level of conscious	Death (multiorgan dysfunction following septic shock)
McGinn et al. [39]	56	F	Non-convulsive myoclonic seizures	NR	MDZ, LEV, PTB	Unclear (1 day)	0.1 mg/kg/hour	Unclear (24 hours)	PTB	Yes	Myoclonic seizures occur approximately 1 every 2 seconds	Seizure frequency was decreased	Improved	None
	57	F	Subtle NCSE	Generalized seizure	PHT, PRO, PTB	13 days	0.5 mg/kg/hour	19 days	Pentobarbital	Yes	EEG showed signs of encephalopathy but no epileptiform discharges	Achievement of burst suppression on EEG	General improvement	None

Continued

Authors and year	Age and sex		RSE type	Etiology	Previous treatment/ anesthetic	Mean RSE duration before KE infusion (range)	Mean KE dosage (mg/kg/hour)	Mean duration of receiving KE	Co-therapy treatments	Clinical response	EEG before KET	EEG after KET	Clinical outcome	Adverse events
Dillien et al. [40]	27	F	GTCSE	Encephalitis	MDZ, PRO, KET (1 m/kg bolus and continuous infusion of 2.5 mg/kg/hour)	31 days	Bolus of 2 mg/kg followed by 5 mg/kg/hour	2 days	PRO	Yes	focal ictal discharges	Reappearance of a 5- to 6-Hz irregularly shaped basal activity	Improvement	Episodes of electrical seizures
Talahma et al. [41]	37	F	Subtle SE	Epilepsy	PRO	3 days	100 mcg/kg/minute	7 days	PRO	Yes	Showed right hemisphere focal SE	Seizure suppression	General improvement	NR
Koffman et al. [42]	72	F	NCSE	NR	LEV, PHT, MDZ	4 days	0.07 mg/kg/hour	Unclear	NR	None	NR	NR	Cardiac arrest	AF, one episode of SBD, three episodes of AS
Vallecoccia et al. [43]	34	M	GNCSE	NR	LEV, PHT, PRO infusion, MDZ, valproate	6 weeks	NR	2 weeks	Unclear	None	Showed generalized no continuative seizure	Showed epileptic activity	Seizure resolution	None
Pediatric														
Yousif et al. [44]	7	M	Subclinical seizure	Epilepsy	PHT, Keppra	Unclear (few minutes)	one dose at 1 mg/kg	N/A	PHT	Yes	Showed a subclinical seizure.	NR	Seizure resolution	None

ASM, anti-seizures medication; CBZ, carbamazepine; CLZ, clonazepam; CPS: complex partial seizures; CSE: Convulsive status epilepticus; F: Female; GBP: gabapentin; GCTC, generalized convulsive tonic-clonic seizures; GTCS: generalized tonic-clonic seizures; GTCSE: generalized tonic-clonic status epilepticus; GBP: gabapentin PB: phenobarbital; PHT: phenytoin; PRO: propofol; PTB: pentobarbital; KET: Ketamine; LEV: levetiracetam; LCM, lacosamide; LZP: lorazepam; M: Male; MDZ: midazolam; NCSE: nonconvulsive status epilepticus; NORSE, new-onset refractory status epilepticus; PER, perampanel; PGB, pregabalin; PRIS, propofol-related infusion syndrome; SE, status epilepticus; THP, thiopental; TPM, topiramate; VPA: valproic acid; AF = atrial fibrillation, one episode of SBD = sinus bradycardia, three episodes of AS = asystole.

Table 4. *Presentation of cases for adults and pediatric population: case series and cohort studies.*

Authors and year	Patients	*N*	Mean Age	Sex (% F	RSE type	Etiology	Previous treatment/ anesthesia	Mean RSE duration prior to KE infusion (range)	Mean KE dosage (mg/kg/ hour)	Mean duration of receiving KE	Co therapy treatments
Case series											
Synowiec et al. [31]	Adult	11	Mean age 52 years (SD 18.0)	36% female	6/11 (55%) were NCSE, and 5/11 (45%) were in GCSE	Low AED levels (3/11; 27%), infection (7/11; 64%), and metabolic disturbance (1/11; 9%).	PRO (64%), LZP(9%), PTB (9%), MDZ (9%), or MDZ + PRO (9%)	Range 1-11 days (mean = 5, SD = 5.1)	Range, 0.45-2.1 mg/kg/hour	Range, 4-28 days (mean = 9.8, SD = 8.9)	CBZ, VPA, LZP, PHT, TPM, PRO, KET, PB, VPA
Basha et al. [46]	Adult	11	Range 33-68 years (mean 54 years)	54%	SPSE (2/11), NCSE (1/11), CPSE (8/11), SG (7/11)	Identified in all except patient 7 (50 years, female) and patient 8(42 years, female)		Mean 5.4 days, standard deviation (SD) 4.0	Range 1-5 mg/kg/h (mean = 3.5 mg/kg/hour)	2-27 days	NR
Höfler et al. [48]	Adult	42	Median 67 years (Q1 59.3, Q3 72.0)	33.3%	Comatose NCSE 67% (28/42), myoclonic SE 14% (6/42), tonic-clonic SE 14% (6/42), focal motor SE 5% (2/42)	Post anoxic encephalopathy 33% (14/42), cerebrovascular 17% (7/42), central nervous system (CNS) infection 10% (4/ 42), CNS tumor 7% (3/42), and unknown in 17% (7/42). 7 (17%) had a previous history of seizures	(17/42) 40% received propofol	3 days (Q1 2.0, Q3 6.8)	Median 2.39 mg/kg/hour (Q1 1.52 to Q3 3.02)	Median 4 days (Q1 2.0, Q3 6.8)	Propofol (35% of patients)
Alkhachroum et al. [49]	Adult	68	53 ± 18 years	46%	Nonconvulsive semiology in 50/68	Acute onset (28/68), Cardiac arrest (18/68), NORSE (11/68), Ischemia/ ICH/SAH (11/68), Infection (8/68)	MDZ	Median 2 days (1-4.5 days)	Mean 2.2 ± 1.8 mg/kg/hour	Median 2 (1-4) days	MDZ (68/68), propofol (36/68), pentobarbital (10/68)
Dericioglu et al. [51]	Adult	7	Range 44-86 years	43%	NCSE in 6 patients, except possible NCSE in one patient	The most common was encephalitis	MDZ in six patients, propofol in two patients, thiopental in one patient	Range 4-19 days	Range 1-5 mg/kg/hour	Range 3-24 days	NR
Caranzano et al. [52]	Adult	11	Mean 48 ± 22 years	45%	NR	NR	NR	Median 4 days (range: 2-20)	Median 5 mg/kg/hour (range: 2.5-15)	Median 2 days (range 1-16 days)	NR
DeVine et al. [50]	Pediatric	3	Mean 47 days	67%	Focal SE in patient 1, NR in other patients	Abusive head trauma, ischemic stroke, and ischemic injury status post cardiac arrest.	LZP, PB, MDZ, PHT	7 days (patient 1), 2 days (patient 2), NR (patient 3)	Mean 1 mg/kg/hour	Mean 5 days	MDZ, PTB
Gaspard et al. [45]	Pediatric (20%), Adult (80%)	58	Median 24 years, range (7 months-74 years)	50%	GCSE 14 (23%), (Tonic-clonic 5 (8%), Myoclonic 6 (10%), Tonic 3 (5%)), GNCSE 3 (5%), FCSE 4 (7%), FNCSEV38 (63%), SE of infantile spasms 1 (2%)	Unknown 34 (57%) acute symptomatic 20 (33%), remote symptomatic 6 (10%)	NR	Median 9 days, range 0-122 days	median 2.75 mg/kg/hour, maximum 10 mg/kg/hour	Range 6 hours to 27 days	NR

Authors and year	Patients	N	Mean Age	Sex (% F	RSE type	Etiology	Previous treatment/ anesthesia	Mean RSE duration prior to KE infusion (range)	Mean KE dosage (mg/kg/ hour)	Mean duration of receiving KE	Co therapy treatments
Sabharwal et al. [47]	Pediatric and Adult	67	8-85 years (mean is 58 years)	73%	NR	Anoxic brain injury (13, 19%), CVA-ischemic (5.9%), CVA-hemorrhagic (4.5%), metabolism (27%), infectious- CNS (7.5%), infectious-systemic (7.5%), autoimmune (4.5%), tumor (4.5%), genetic(3%), unknown etiology (16%)	Propofol in 61 patients (91%)	NR	25-175 mcg/kg/minute	Mean 6 days (1-29 days)	Propofol
Cohort studies											
Keros et al. [53]	Pediatric	48	Median 7 years (Q1 2 years-Q3 11 years)	40%	NR	NR	MDZ	NR	NR	Median 7 years (Q1 4 years-9 years)	98% of patients received MDZ, 100% received Pentobarbital
Jacobwitz et al. [54]	Pediatric	69	Median 0.7 years (IQR 0.15-7.2 years)	48%	NR	Acute neurologic injury in 22 patients (32%) (hypoxic-ischemic encephalopathy in 14/22, stroke in 4/22, and traumatic brain injury in 4/22)	MDZ on 45% of patients, pentobarbital	Median 20 hours (IQR 10.8-45.3 hours)	max was 7 mg/kg/hour (3%), 6 mg/kg/hour (4%), 5 mg/kg/hour (7%), 4 mg/kg/hour (13%), 3 mg/kg/hour (20%), 2 mg/kg/hour (22%), and 1 mg/kg/hour in 29% of patients	Median 85.7 hours (IQR 49.7-128.0)	MDZ, Pentobarbital, Isoflurane

26 days [46] to 6 weeks [43]. Propofol and MDZ were the anesthetics commonly delivered alongside KET. An illustration is in Höfler et al. [48], where 15% (4 of 27 patients) received (S)-KET alongside propofol.

Efficacy

Among case reports, the efficiency of KET treatment was analyzed based on how fast and impactful the anesthetic was able to calm or completely resolve SE seizures. The patient's condition after KET admission was mainly determined using the EEG. In most cases, KET seemed to be effective in immediately reducing the frequency, amplitude, and duration of seizures [31,35,37,38,42,50] and promoting burst suppression on EEG [31,36,42,43,50,51]. Though in some cases, the impact was not immediate [39,46,51,52,43]. The lowest recorded time for seizure cessation was 3 minutes in Yousif et al. [44] while using an IV of 1 mg/ kg. In Kramer [35], cessation was achieved after 12 hours of admission with the dose at 3.3 mg/kg/hour. In the second case in Zeiler et al. [36], this happened in 30 minutes. Also, 12 days in Esaian et al. [37] and 24 hours in Shrestha et al. [38].

When analyzing data, it was noted that the time from SE onset to KE admission probably affected the response rate. Gaspard et al. [45] and Jacobwitz et al. [54] both agreed that the response rate for patients was higher when KET was introduced in the early seizure stage. In Jacobwitz et al. [54], 73% and 20% of those who had positively responded to KET were those treated 0-6 and 6-2 hours after SE onset. Apart from the time of admission, the response also seemed to be dependent on the age/physical wellness of the patient, the number of initial treatments, and the sequence of administering KET. In Gaspard et al. [45], there was hardly any positive response in cases where KET infusion rates were less than 0.9 mg/kg/hour [45]. Also, in cases where seven or more failed treatments, KET seemed not to be that impactful [45]. When administered as a first anesthetic, the termination rate was 61%, and when administered after MDZ as the first anesthetic, the termination rate became 29% [54]. Jacobwitz et al. [54] also noted that seizures seemed to terminate when the dose was 2 mg/kg/hour (IQR 1-3) and persisted when the dose was 3 mg/kg/hour (IQR 2-4).

In Gaspard et al. [45], there was complete seizure resolution in 34 cases (57%) of SE. In Basha et al. [46], KET ultimately terminated SE in four patients (36%) and controlled it in 73% of the study population. The response/ control rate in Sabharwal et al. [47] was 91%. Alkhachroum et al. [49] showed a 65% seizure cessation after withdrawal of KET and 79% cessation (control) within 24 hours of administering KET. In Dericioglu et al. [51], the response rate was 71%. In Caranzano et al. [52], SRSE control was achieved in 63.6% (7/11) of patients, and the resolution was in 27.3% (3/11) of patients. Jacobwitz et al. [54] had a response rate of 74% at the end of the study; there was a 46% termination rate and a 28% reduction rate (Table 4).

Outcome

The outcome among patients also varied greatly. Some were discharged home, others to critical care,

Table 5. *Clinical Outcome for case series and cohort studies.*

Authors and year	Clinical response	EEG before KET	Clinical outcome	Adverse events
Synowiec et al. [31]	Yes (4/11)	NR	RSE resolution 4 (36%), RSE managed in 73%	NR
Basha et al. [46]	Yes (4/11)	NR	RSE resolution 4 (36%), RSE managed in 73%	NR
Höfler et al. [48]	Yes (27/42)	NR	KEA treatment was generally effective; overall mortality was 45.2%	None
Alkhachroum et al. [49]	50% in 24 hours and 63% at the end	Focal seizures on EEG in 57 patients (39%)	in-hospital mortality was 46%	NR
DeVine et al. [50]	Yes (Patient 2)	evidence of focal seizures (patient 1), NR (patient 2), identified multifocal seizures (patient 2)	NR	None
Dericioglu et al. [51]	Yes, in six patients, no in one patient	NR	NCSE was controlled in 6 patients; KET was effective in 57%-71%	None
Caranzano et al. [52]	Yes [SE controlled in seven patients (63.7%)]	NR	Permanent SE control in 3 patients (27%), death in 4 patients (36.4%)	6 patients (54.5%) had a new handicap
Sabharwal et al. [47]	NR	NR	SRSE resolution rate was 91%, and the mortality rate was 39%	None
Gaspard et al. [45]	In 60% of episodes	NR	34 episodes (57%) were controlled, and the mortality rate was 45% (26 of 60)	18 episodes (30%)
Keros et al. [53]	NR	NR	14 patients (29%) died in the hospital	NR
Jacobwitz et al. [54]	Yes [seizure termination in 32 patients (46%), seizure reduction in 19 patients (28%)]	NR	seizure termination in 32 patients (46%), 35% of patients had new or worse epilepsy, 21 patients (30%) died in hospital	In three patients (4%)

and others to rehabilitation (inpatient or outpatient). In Kramer [35], the patient was discharged from ICU 24 hours after anesthetics had been weaned off and 12 days after admission. After 3 weeks in rehabilitation, the patient was discharged home. In Zeiler et al. [36], the rehabilitation period was 2 months. In Synowiec et al. [31], two patients (18%) were discharged home, three patients (27%) to a long-term acute care facility, one patient (9%) to a skilled nursing facility, and three patients 27% to an inpatient rehabilitation clinic. Three patients in Basha et al. [46] were discharged home, and five were discharged to an acute rehabilitation or skilled nursing home [46]. 23 (48%) patients in Jacobwitz et al. [54] were disposed to an acute care facility, 10 (21%) to rehabilitation, 10 (21%) home, 1 (2%) to an extended living facility, and 2/48 (4%) remained in an ICU. Some patients were discharged, but there are also reported mortality rates across the included studies. One patient in Shrestha et al. [38], patient 2, died due to a multiorgan dysfunction caused by septic shock. Also, Synowiec et al. [31] recorded two deaths for medical causes unrelated to KET admission. In Gaspard et al. [45], the overall mortality rate was reported as 45%, i.e., 26 of 60 patients. There were three deaths in Basha et al. [46] due to worsening intracranial hemorrhage [2] and cardiac arrest [1]. The recorded mortality rate for Sabharwal et al. [47] was 39%, mostly due to anoxic brain injury and other severe medical/neurological diseases like cardiac arrest and liver failure. The mortality rate was 45.2% in Höfler et al. [48] mostly due to cardio-respiratory failure. In Alkhachroum et al. [49], the mortality rate was reported according to the treatment outcome of KET. Of patients whose seizures had ceased, 18 (41%) of them died, and for patients without seizure cessation, 13 (54%) of them died. The authors did not link the probability of death to seizure cessation after KET withdrawal [49]. One patient out of three (33%) died in DeVine et al. [50]. The mortality rate was 29% in Dericioglu et al. [51], it also attributed to other medical complications. Caranzano et al. [52] had a mortality rate of 4 (36.3%) at discharge. Jacobwitz et al. [54] had a mortality rate of 30% (21 patients); this was attributed to the withdrawal of technological life support and systemic medical and neurologic conditions.

Recurrence

Reports of seizure recurrence were not common across included studies, and those present were vaguely presented. In Dillien et al. [40], after 48 hours of KET infusion and the patient showing improved reactivity, there was a recurrence of episodes of electrical seizures. These, however, resolved when the dosage of KET was increased. There was one case of recurrence in Basha et al. [46]. In Caranzano et al. [52], it was reported that only 27.3% of people did not have a relapse. Hence, it may be assumed that the rest is represented by a case of recurrence.

Adverse events

Apart from death, there were some adverse outcomes reported by several studies. However, none of the studies found any connection between the adverse event and using KET to treat SE. Some of these events occurred in Koffman et al. [42] where the patient suffered an episode of atrial fibrillation with a rapid ventricular response, an episode of sinus bradycardia, and three episodes of brief asystole. Vallecoccia et al. [43] reported dystonia

and numbness of the lower limbs. In the case study by Gaspard et al. [45], 33% of patients developed sepsis, shock, organ failure, and pneumonia complications. In case 1 in DeVine et al. [50], the patient suffered significant hypoglycemia. In Dericioglu et al. [51], 1 patient developed hepatic failure, and 16 out of 46 patients in Jacobwitz et al. [54] developed new or worse epilepsy at discharge.

Limitation

Overall, despite yielding insightful inferences on KET's efficacy and related adverse effects in RSE and SRSE, our review has ignificant limitations. First, the number of studies identified is limited and a large number (90%) of these studies are case reports and case series with small sample sizes, which reduces the generalizability of our study. Also, all studies have no significant and enough data to perform a meaningful meta-analysis. The heterogeneity of the treatment protocols used across studies also limits our ability to suggest a standard KET dosing strategy for either adult or pediatric RSE patients. Also, for all patients receiving many medications concomitantly with KET, it is possible that seizure cessation may have been related to a cumulative or delayed effect of the co-administered or previously administered medications. Nevertheless, despite these limitations, this review successfully compiles current KET use patterns, documents KET's rapid efficacy in treating RSE, and appears to be safe in the pediatric and adult populations.

Conclusion

A research question was presented at the beginning of this article, and data from 21 studies were reviewed to answer that research question. The admission of KET as management for RSE and SRSE has been shown to be effective in controlling and terminating SE seizures. However, some factors appear to impact the response produced by KET treatment. These factors are dose, duration from SE onset to KET infusion, and the sequence of use/duration and number of initial treatments. KET presented to generally be safe, as there are a few reported negative events. The mortality rates seemed to be high, but none of the studies reported any direct link between these adverse outcomes and using KET to manage SE.

Recommendation

In support of Rosati et al. [8], this article calls for new studies and clinical trials specifically designed to understand the effect and safety of using KET in the management of SE.

Conflict of interest

The authors declare that there is no conflict of interest regarding the publication of this article.

Funding

None.

Consent to participate

Not applicable.

Ethical approval

Not applicable.

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