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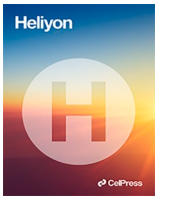

Research article

Ketamine: Pro or antiepileptic agent? A systematic review

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ABSTRACT

Purpose: of Review: This evidence-based systematic review evaluated the safety of ketamine as regard the potential to provoke epilepsy to help better guide anesthesiologists in their practice.
Recent findings: Ketamine, originally developed as a dissociative anesthetic, has gained attention for its potential therapeutic applications in various medical conditions, including epilepsy. Ketamine is generally well-tolerated and widely used in anesthesia, however, conflicting data are confusing the anesthesiologists regarding the potential risk of seizures associated with its use. The literature that claimed the proepileeptic property are inconsistent and the mechanism of action is unclear. Moreover, the case reports had been in same certain contexts, such as procedural sedation where ketamine was used as a single agent. On the other hand, the retrospective data analysis confirmed the positive role ketamine plays as antiepileptic agent.
Summary: Many studies have shown promising results for the use of ketamine as antiepileptic agent. In case of epileptic patients, there is no contraindication for using ketamine, however, combining with benzodiazepine or propofol may enhance the safety.

1. Introduction

Extensive studies have been conducted on the pro-and-anticonvulsant properties of anesthetics related to effects on the brain [1]. The impact of having epileptogenic effects is of concern, especially under anesthesia where epilepsy may go unnoticed in an anesthetized and paralyzed patient with the potential for deleterious neuronal injury [2]. Moreover, the epileptogenic effects may extend to the postoperative period when seizures may occur in less controlled circumstances than in the operating room which could exaggerate harmful effects. Therefore, in seizure-susceptible patients, the use of potentially epileptogenic anesthetics in clinical practice it typically avoided.

Ketamine was first used in humans in 1965 by Corssen and Domino [3]. Ketamine manifests clinical effects through effects on different receptors, including *N*-methyl-D-aspartate receptors (NMDAR), opioid receptors, and monoaminergic receptors [4]. In

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addition, it shows different effects in various clinical scenarios according to the dose used. This makes ketamine a versatile agent for intravenous anesthesia, sedation, multimodal analgesia, and antidepressant effects [5–7]. It has been believed that ketamine can elicit seizures in patients with epileptic diathesis [8]. However, ketamine has also been utilized clinically to control status epilepticus [9]. At present, ketamine is still controversial, therefore, this comprehensive review focuses on the safety of ketamine in anesthesia management of epileptic patients.

1.1. Mechanism of action of ketamine

Ketamine acts at multiple receptors, resulting in various actions.

1. **N-methyl-D-aspartate (NMDA) Receptors**: Ketamine is a racemic mixture containing equal parts of (R)- and (S)-ketamine, with the (S)-enantiomer possessing stronger affinity for the NMDA receptor [10]. Ketamine blocks NMDA receptors as it is considered a non-competitive NMDA receptor channel blocker, which contributes to potent anesthetic and analgesic properties [11,12]. Ketamine's interaction with NMDA receptors is also thought to contribute to antidepressant effects [13].
2. **Opioid Receptors**: It has been reported that the interaction between ketamine and mu-opioid receptors (MORs) is equivalent to the interaction between ketamine and NMDA receptors [14]. This interaction can produce antidepressant effects by enhancing serotoninergic pathways that inhibit or attenuate decline [15,16].
3. **Monoaminergic Receptors**: Ketamine interacts with monoaminergic receptors. This interaction raises the number of serotonin 1B receptors, hence increasing dopamine levels in the brain. The interaction with monoaminergic receptors is also thought to contribute to ketamine mediated or modulated antidepressant effects [17].
4. **Muscarinic Receptors**: Ketamine interacts with muscarinic receptors, and this interaction may contribute to described cognitive side effects of ketamine [18].
5. **Voltage-Sensitive Ca Ion Channels**: Ketamine interacts with voltage-sensitive Ca ion channels, resulting in ketamine mediated or modulated analgesic effects [19].
6. **Hyperpolarization-activated cyclic nucleotide channels (HCN1) Receptors**: The hypnotic effects of ketamine appear to be primarily mediated by inhibition of NMDA and HCN1 receptors [12].

1.2. Methods

In the present investigation, a systematic search was performed of the following online databases; (Cochrane, WOS, PubMed, Scopus) using the following search strategy; (Epilepsy OR Epilepsies OR "Seizure Disorder" OR "Seizure Disorders" OR "Awakening Epilepsy" OR "Epilepsy, Awakening" OR "Epilepsy, Cryptogenic" OR "Cryptogenic Epilepsies" OR "Cryptogenic Epilepsy" OR "Epilepsy, Cryptogenic" OR Fits AND Ketalar OR Ketaset OR Ketanest OR Calipsol OR Kalipsol OR Calypsol OR Ketamine). We used the title

Table 1
Ketamine as pro-epileptic agent.

	Article	Groups Studied and Intervention	Results and Findings	Conclusions
Effects of ketamine in epilepsy	(Celesia et al., 1975)	Ketamine was administered intravenously to 26 epileptics and the effects of ketamine on the patients' clinical seizures and electroencephalograms were compared with similar periods during alert and sleep states.	17 (65 %) showed epileptic discharges in their alert electroencephalograms. Sleep exacerbated epileptic discharges in 15 cases (58 %), while ketamine did so in eight cases (31 %). No seizures were observed during ketamine anesthesia	Ketamine neither precipitates nor aggravates seizures and is less effective than natural sleep as an activator of epileptic discharges.
Ketamine and epilepsy	(Corssen et al., 1974)	comparing the impact of ketamine on the electroencephalogram (EEG) of healthy human volunteers without epilepsy history and those with a history of active epilepsy.	Ketamine does not trigger seizure discharges in individuals without epilepsy or cause any EEG changes that indicate seizure activity in patients with a history of epilepsy and a normal EEG. While it is possible for an abnormal EEG to worsen under ketamine, this occurrence is rare.	Although the authors did not find any indication that ketamine can cause generalized convulsions in epileptic patients, caution should be exercised when using ketamine during anesthesia for susceptible patients.
Anesthesia and epilepsy	(Perks et al., 2012)	A review article studying the effects of various anesthetic drugs, including ketamine, on causing seizures were investigated.	Similar to other intravenous drugs, small doses of ketamine can promote seizures.	When administered in doses that induce sedation or anesthesia, ketamine exhibits anticonvulsant qualities.
Ketamine, at low dose, decrease behavioral alterations in epileptic diseases induced by pilocarpine in mice	(Tannich et al., 2020)	A study evaluating the impact of administering a small amount of intraperitoneal ketamine (10 mg/kg) on behavioral impairment and acute neuronal death in the cerebral cortex during the acute phase in a model of epileptic mice before and after pilocarpine injection was examined.	Administering a low dose of ketamine to mice reduced clinical symptoms such as movements of the vibrios, nods of the head, and movements of the whiskers, especially when given before epilepsy induction.	The reason behind these results could be attributed to the inhibition of NMDA receptors by ketamine but it needs further evaluation.

Table 2
Ketamine as an antiepileptic drug.

	Article	Groups Studied and Intervention	Results and Findings	Conclusions
	(Golub et al., 2018)	Two case reports and a systematic review of the use of high-dose ketamine infusion in RSE	Ketamine was successful in terminating the electro-clinical presentation of seizures. Burst suppression was noted in both cases. The article also identified one systematic review during their search	Ketamine is effective in terminating seizure activity
Ketamine use in pregnancy	(Talahma et al., 2018)	A case report of a 37 yo woman with epilepsy secondary to astrocytoma that was surgically resection followed by radiation and chemotherapy. Ketamine was administered from D3-9 of her seizures as a bolus of 80 mg followed by continuous infusion at a rate of 100 mcg/kg/min. Seizures stopped 9 h after ketamine initiation. No effects on the fetus, delivery, or developmental milestones up to 38 weeks after delivery.	In contrast to previous studies, ketamine did not affect fetal maturation or the future infant's mood or cognitive function.	Ketamine can be effective as well as safe to use in pregnant women presenting with status epilepticus.
Systematic Review for ketamine for RSE	(Rosati et al., 2018)	Systematic review of the use of ketamine for refractory status epilepticus	No randomized controlled trials were found 27 case reports with 30 cases and 14 case series, 6 including children were found	The available evidence of using ketamine is of poor quality.
Ketamine for burst suppression in substance use induced seizures	(Mutkule et al., 2018)	A case report of an 18 years old man presenting with cannabis-induced SRSE	Ketamine IV 1 mg/kg bolus followed by 2 mg/kg/h infusion for 48 h resulted in burst suppression	Ketamine was useful in treatment of SRSE resulting from cannabis use
Ketamine implicated in cardiac events	(Koffman et al., 2018)	A retrospective review for 9 ICU patients in a tertiary care center.	A 72 years old woman with subarachnoid hemorrahge developed serious cardiac complications; she developed atrial fibrillation with rapid ventricular response followed by sinus bradycardia and three brief asystole.	Ketamine should be used with caution in patients with subarachnoid hemorrhage.
Ketamine for RSE associated with anti-NMDA encephalitis	(Santoro et al., 2019)	Three case series of patients presenting with anti-NMDA encephalitis and RSE.	Seizures in all three patients responded to the addition of ketamine IV. One case expired 14 days after starting ketamine for an unexpected cardiac arrest.	Ketamine could be considered as an effective treatment in anti-NMDA associated encephalitis.
Low dose IV ketamine transition to oral ketamine	(Borsato et al., 2020)	Clinical case report and literature review. Patient is 21 yo M with 4-year-history of multifocal drug resistant epilepsy (DRE), had resection of pilocytic astrocytoma, and then presented with tonic clonic seizures on postoperative day 5. IV ketamine 0.5 mg/kg/h led to cessation of seizure activity. He was then transitioned to oral ketamine with good effect after titration of dose to 500 mg twice daily. He then was discharged on ketamine 300 mg three times daily, phenytoin 150 mg three times daily, phenobarbital elixir 176 mg twice daily, and brivaracetam 100 mg twice daily.	No results for literature review for low dose ketamine in management in status epilepticus in humans.	Low dose ketamine (0.25–0.5 mg/kg/h) may be considered for acute provoked worsening of DRE and could avoid unwanted respiratory and cardiac depression. Transitioning from IV to oral ketamine could potentially decrease length of stay in ICU.
Ketamine for refractory neonatal seizures	(Huntsman et al., 2020)	A case report of neonatal RSE. Ketamine was used at 0.5 mg/kg/hr and dose increased to 1 mg/kg/hr	Burst suppression pattern occurred after use of ketamine.	Ketamine could be considered for neonatal refractory seizures.
Ketamine for Super refractory SE associated with Alternating Hemiplegia of Childhood	(Samanta, 2020)	A report of two cases with documented molecular evidence of AHC (female with E815K and male with D801 N) presented for Super refractory SE with controlling of seizure after starting IV ketamine	Seizures were controlled in both subjects.	Early ketamine use could be considered for treatment of AHC related SE. Further research is needed to determine if ketamine can induce neuronal cell death or alter neurogenesis.

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Table 2 (*continued*)

	Article	Groups Studied and Intervention	Results and Findings	Conclusions
Ketamine infusion in adults	(Alkhachroum et al., 2020)	Retrospective analysis of 261 adult patients admitted to neurologic intensive care unit with supra-refractory status epilepticus. 68 patients of which received ketamine and midazolam (Average infusion of Ketamine 2.2 ± 1.8 mg/kg/h with median duration 1–4 days with additional midazolam).	55 patients (81 %) had at least 50 % decrease in seizure burden in 24 h, 43 (63 %) had seizure cessation. After stopping ketamine, 54 (79 %) had at least 50 % decrease in seizure burden and 44 (65 %) had complete seizure cessation. 18 (41 %) patients died after seizure cessation with ketamine and 13 (54 %) patients died after no seizure cessation with ketamine. Cardiac arrest was the most common etiology for seizures (27 %). 2 ± 1 concurrent anesthetics (propofol in 36 patients and pentobarbital in 10 patients) were used for SRSE treatment.	Ketamine infusion showed to be effective for treatment of SRSE. High dose ketamine appear to be effective with improved hemodynamics and no effect on intracranial pressure (ICP)
Ketamine in pediatric population	(Sperotto et al., 2021)	Retrospective review of clinical charts for patients receiving ketamine >24 h between 2017 and 2018	60 pediatric patients were included, 4 % (N = 2) of which was for epilepsy had cessation of seizures after initiation of ketamine	Ketamine has a potential in treatment of RSE.
Early combination of ketamine and midazolam	(Choi & Shin, n. d.)	A report of two cases with RSE and hemodynamic instability	Both cases received ketamine + midazolam with effective suppression of epileptic discharge and less hemodynamic instability.	Combining ketamine and midazolam could be effective in patients with hemodynamic instability.
Ketamine in Non-Convulsive Status Epilepticus	(Dericioglu et al., 2021)	A retrospective chart review study for a patients treated for RSE/SRSE in a single center.	The study included 7 patients. Ketamine was definitely effective in 4/7 and possibly effective in 1/7. Earlier initiation correlated with higher efficacy ($p = 0.47$)	Ketamine was effective in controlling R/SR NCSE in a considerable number of patients in the study
Ketamine in pediatric population	(Howing et al., 2022)	A case report of ketamine use in a 9-month-old for girl for RSE	Ketamine was successful in controlling electro-clinical presentation of seizures.	Ketamine could be considered for pediatric RSE.
Ketamine combined with Perampanel	(Manganotti et al., 2021)	A case report of a 23 years old man who developed SRSE following motor vehicle accident.	Oral Perampanel 16 mg via nasogastric tube along with ketamine loading (1.5–3 mg/kg) followed by infusion (2–10 mg/kg/h) produced burst suppression in EEG	Combining Ketamine and Perampanel could be effective in treating of SRSE
Ketamine infusion in children	(Benini et al., 2021)	Narrative review of studies about use of ketamine in pediatric population in different care settings.	7 observational studies assessed ketamine for analgesia with favorable results. 1 clinical trial assessed rectal ketamine administration in children with cerebral palsy with moderate sedation and analgesic effect. 1 retrospective clinical study was performed to evaluate ketamine treatment in refractory status epilepticus in children in intensive care unit. Study included 18 children with refractory status epilepticus in Beijing Children's hospital with 2 groups: first group: loading-maintenance (7 patients), second group: maintenance (11 patients). RSE was controlled in all patients from first group and in 4 of second group. Another retrospective study adopted IV ketamine infusion, 9 children treated with ketamine infusion had 70 % successful response, The median dose of ketamine in	Refractory status epilepticus was controlled with ketamine in the majority of patients, showing a significantly greater effectiveness in the loading-maintenance protocol (Loading dose 1.5 mg/kg, 2.2–2.4 mg/kg/hr) compared to the maintenance group **(needs rephrasing).** Ketamine administration in children with RSE prevented the use of endotracheal intubation (a factor leading to worsening of RSE)

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Table 2 (*continued*)

	Article	Groups Studied and Intervention	Results and Findings	Conclusions
			continuous i.v. infusion was 40 μg/kg/min. None of the patients experienced serious adverse events. Another ongoing multicenter, randomized, controlled study in Italy to assess efficacy of ketamine vs. conventional antiepileptics in treatment of RSE in children (57 patients enrolled) with no available results.	
Ketamine caused abdominal compartment syndrome	(Natteru et al., 2022)	A case of 74 years old male with SRSE treated with ketamine bolus (0.5 mg/kg) followed by infusion of 1 mg/kg/h with a maximum of 7.5 mg/kg/h	EEG showed suppressed delta waves. Patient had abdominal compartment syndrome starting at 25 h after starting infusion of maximum ketamine dose.	Ketamine could result in abdominal compartment syndrome.
Ketamine in refractory status epilepticus	(Brisca et al., 2022)	A case reported of 4-month-old girl with hemimegalencephaly (HME) and intractable seizures since birth resistant to multiple antiepileptics including repeated bolus of midazolam 0.2 mg/kg, levitracetam 30 mg/kg, and continuous IV midazolam infusion of 0.15 mg/kg/h. Ketamine then was administered at loading dose of 1 mg/kg followed by continuous infusion at incremental dose up to 1.7 mg/kg/h with maintained continuous infusion of midazolam at 0.1 mg/kg/h. Seizure burden was reduced to more than 80 % within 24 h with stable respiratory and hemodynamic conditions.	Ketamine with midazolam was effective in controlling resistant seizures with HME until time of surgery.	Ketamine could be effective in controlling HME-associated refractory seizures
Ketamine for neonatal and pediatric RSE	(Jacobwitz et al., 2022)	A retrospective single-cohort study of patients admitted to ICU at a quaternary care children's hospital	69 patients were treated with ketamine infusion for RSE with seizure termination occurring in 32 patients (46 %). Burst suppression occurred in 1 (1 %)	Ketamine could be beneficial in neonates and children with SE.
Double anti-glutamatergic for SE	(Souidan et al., 2022)	A case series for patients with status epilepticus (wither convulsive or non-convulsive) who received either ketamine alone or in combination with Perampanel (PER).	Burst suppression pattern occurred in 75 % of patients receiving ketamine + PER in comparison to 28.5 % for patients in ketamine alone.	Dual anti-glutamatergic regimen could be considered for status epilepticus
Ketamine vs. conventional anesthetics in pediatric RSE	(Rosati et al., 2022)	A multicenter, randomized, controlled, open-label, sequentially-designed, non-profit Italian study to assess ketamine efficacy in RCSE in children. Recruited subjects were randomized to either the experimental arm (Ketamine IV up to 100 μg/kg/min) or the control arm (midazolam (MDZ) up to 12 μg/kg/min and propofol (PR) up to 5 mg/kg/h and/or thiopental (TPS) up to 6 mg/kg/h).	Only 10/76 children were enrolled in the five-year period, with 2/5 in experimental arm successfully treated with ketamine and 2/5 successfully treated with thiopental Study was prematurely terminated for low eligibility of patients and no successful recruitment.	No conclusions could be drawn about the objective of the study. The following reasons were hypothesized to be the causes of the study failure: a) too rigid protocol, b) involvement of too many different participant actors; emergency department clinicians, neurologists, and intensivists, c) non-profit nature
Prehospital use of ketamine in Benzodiazepine-resistant seizures	(Perlmutter et al., 2023)	A case series of 6 pediatric patients presented with benzodiazepine-resistant seizures who were treated with ketamine by emergency medical services (EMS) personnel before presentation to the hospital	Ketamine was effective in controlling motor signs of seizure activity in all six patients.	Ketamine could be safe and effective to use in pediatric population for prehospital management of RSE.
Ketamine infusion as an adjunct in young infants	(Devine, 2023)	A case series of 3 young infants with RSE and SRSE who received ketamine infusion in conjunction with other antiepileptics to control seizures.	Ketamine was effective as an adjunctive medication to control the electro-clinical presentation of seizures in 3/3 infants.	Continuous ketamine infusion could be considered for infantile RSE and SRSE after failure of first and second line modalities.
Ketamine as second line for benzodiazepine-refractory convulsive status epilepticus in children	(Buratti et al., 2023)	Review of most recent and significant publications on the potential role of ketamine in the treatment of Status Epilepticus.	1 retrospective study of 58 patients (46 adults and 12 children) showed 57 % seizure resolution and 32 % seizure halting due to ketamine	Evidence of use of ketamine in SE is restricted to case reports and case series.

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Table 2 (*continued*)

	Article	Groups Studied and Intervention	Results and Findings	Conclusions
			"possible" or "likely" response. 1 consecutive series of 68 adults led to decrease in SRSE. 1 literature review showed positive effect of ketamine in 248 individuals including 12 children. Ketamine was twice as effective if used early (efficacy rate 64 % in RSE lasting for 3 days and dropping to 32 % in RSE of mean duration of 26.5 days). Ketamine dose did not appear to be an independent factor. 1 retrospective single-center cohort of 69 children treated in neonatal and pediatric ICU showed transient hypertension side effect in two patients, delirium in one patient, seizure termination in 32 (46 %) patients, seizure reduction in 19 (28 %) patients, and no change in 18 (26 %) patients. Ketamine had better chance to be followed by seizure termination if used as first-line anesthetic. No Cochrane systematic review found on ketamine and SE	
Safety of ketamine in RSE in neonates	(Pin et al., 2023)	A case report and systematic review of the use of Ketamine neonatal RSE (total of 8 cases)	Ketamine was successful in controlling electro-clinical seizures. In 5/8 of reported cases, burst suppression was the most frequent EEG finding.	Ketamine could be used as third line treatment for treatment of neonatal RSE.
Factors affecting response to ketamine	(Srinivas et al., 2023)	Retrospective data analysis of 81 patients presented over a 10-year period for treatment of RSE (79 adults + 2 pediatric patients). Ketamine was administered as a bolus in 50 % of patients (median 2 mg/kg/hr) followed by continuous infusion (median 2.43 mg/kg/hr).	In the all patient model: Anoxic brain injury and the presence of a loading dose of ketamine were negative predictors for drug responsiveness History of epilepsy had odds of 3.19 for medication response. In a model that had ketamine-associated seizure cessation only (N = 36), SE duration, loading dose, and ABI were associated with negative outcome. In addition, each additional day of SE decreased the odds of cessation after ketamine by 8 %. ABI, on the other hand, decreased the odds by 91 % 13.6 % of patients required discontinuation of reduction of vasopressors after starting ketamine. Also, 18.5 % of patients developed pulmonary vascular congestion. No changes to intracranial pressure was reported. Also, no changes in ICP in patients with pre-existing intracranial hypertension.	Ketamine is effective in patients with chronic epilepsy and late in the course of their RSE treatment.

and abstract filter across all databases. All the remaining studies after the removal of duplicates were screened by title and abstract, then we did a full text screening to further evaluate which papers to include. All primary studies including animal studies that discuss the role of ketamine as an anti-epileptic or epileptogenic agent were included in our review. We also included previous secondary research such as reviews which support both sides. We excluded any irrelevant studies; which didn't meet our inclusion criteria.

2. Results

We included all the study designs that described Ketamine as an anti-epileptic or as an Epileptogenic agent. Relevant animal studies were also included, including evidence from basic science studies. We used the studies to review different aspects of ketamine as well as its effects related to seizures. There were significantly more studies identified during our study regarding ketamine anti-epileptic effects. Those studies that describe ketamine pro-epileptic activity are described in Table 1. A total of four studies are summarized. Those studies that describe ketamine as an anti-epileptic drug are summarized in Table 2. A total of twenty-six studies are included.

3. Discussion

3.1. Ketamine associated seizure activity

Ketamine has been reported to induce seizures in some cases, which may add to the confusion of clinicians as to its role in patients with a seizure history [20]. The dilemma is challenging, especially when ketamine is the drug of choice in susceptible patients or those with a history of epilepsy. Many conflicting studies have been conducted to prove whether ketamine itself can cause convulsions and stimulate seizure foci or not. However, medical literature describing the convulsant potential of ketamine at present is inconclusive**.** In this regard, various studies have shown that ketamine has anticonvulsant and neuroprotective characteristics [21]. Recent research has demonstrated that ketamine can be utilized to effectively control refractory status epilepticus [22]. McCarthy et al.[23]published the first evidence that ketamine exerts an anticonvulsant effect in animal models in 1965. The notion that ketamine could elicit epileptic alterations, shown in cat models, was quickly disproved in a study with human volunteers. In this study, ketamine did not induce epileptiform discharge in epilepsy patients or normal participants [23,24]. Recently, Ketamine has been proven to exert antiepileptic, neuroprotective, and synergistic effects with other anticonvulsant drugs [22,25]. Although these studies did not mention the doses of ketamine used.

Celesia et al. conducted a study where they administered ketamine intravenously to 26 individuals with a history of epilepsy. They compared their clinical seizures and electroencephalograms during alert and sleep states. In this study, the dose of ketamine is not mentioned and only its intravenous injection is mentioned. The effects of ketamine on the patients' clinical seizures and electroencephalograms were compared with similar periods during alert and sleep states. Out of the total cases, 17 (65 %) showed epileptic discharges in their alert electroencephalograms (EEG). Sleep exacerbated epileptic discharges in 15 cases (58 %), while ketamine did so in eight cases (31 %). However, no seizures were observed during ketamine anesthesia. The study concluded that ketamine does not trigger or worsen seizures and is less effective than natural sleep in activating epileptic discharges [26]. It means that ketamine administration elicited less seizure activity and EEG changes, in comparison to sleep and awake epileptic patients.

Corssen et al.s[25] compared the impact of ketamine on the electroencephalogram (EEG) of healthy human volunteers without epilepsy history and those with a history of active epilepsy. They found that it is possible for an abnormal EEG to worsen under ketamine. However, ketamine did not trigger seizure discharges in individuals without epilepsy. Moreover, ketamine did not cause any EEG changes that indicate seizure activity in patients with a history of epilepsy and a normal EEG. Finally, the study did not provide any evidence suggesting that ketamine is likely to cause generalized convulsions, even in patients with both epilepsy and an abnormal EEG. Surprisingly, there is proof that ketamine can suppress or almost eliminate seizure or seizure-like EEG discharges in epileptic patients during clinical seizures. The study comprised 30 adult patients (10 males, 20 females) ranging in age from 19 to 68 years. Group A consisted of 9 patients whose history and medical records gave no evidence of CNS disorders. Group B consisted of 21 patients with known epilepsy history. Ketamine was administered through the rubber cuff of the infusion line, in a dose of 1 mg./lb. body weight, given in a period of 30 s except for one case in which the experiment was repeated and the dose of ketamine was doubled (case 4). In group A, ketamine-induced EEG changes consisted of the disappearance of alpha waves, the appearance of fast activity in the 30 to 35 per second, or "gamma" range, and the usual appearance of theta-wave activity. Very few patients showed delta waves, but 5 normal control subjects developed an unusual periodic pattern, lasting from 1 to 3 min after the completion of the injection and consisting of quasiperiodic high-voltage complexes of 250 to lo00 msec. In group B, the 5 epileptic patients with a normal EEG, ketamine produced EEG changes similar to those described in the patients of group A. No seizure discharges were recorded. In another 12 patients with borderline or abnormal EEGs, the ketamine induced EEG changes essentially resembled those observed in group A. In particular, no exacerbation or aggravation of preexisting focal or diffuse seizure discharge complexes could be detected. In the remaining 4 cases, there were significant. EEG changes related to ketamine administration, and these warrant detailed discussion. Nevertheless, they advised to apply ketamine cautiously during anesthesia for susceptible patients [27].

In 1965, Perks et al. investigated the potential epileptogenic effects of various anesthetic drugs, including ketamine. They stated that as with other anesthetic drugs, small doses of ketamine might promote seizures. However, when ketamine was administered in doses that induced sedation or anesthesia, ketamine exhibited anticonvulsant qualities [25].

The study was conducted in 2012 on humans. By considering that this is a comprehensive study and all kinds of studies have been compiled to investigate the effects of ketamine (pro-epileptic or antiepileptic), therefore, it is not possible to make a net decision about the definitive effect of ketamine by relying only on one study.

In a separate study conducted in 2020 by Tannich et al. the impact of administering a small amount of intraperitoneal ketamine (10 mg/kg) on acute neuronal death in a model of epileptic mice before and after pilocarpine injection was examined. The researchers discovered that mice treated with ketamine experienced less behavioral dysfunction than others. It was noteworthy that administering a low dose of ketamine to mice reduced clinical symptoms such as movements of the vibrios, nods of the head, and movements of the whiskers, especially when given before epilepsy induction. They attributed it to the inhibition of NMDA receptors by ketamine [28].

There is controversy regarding use of ketamine as general anesthetic agent in patients of epilepsy. Both pro and antiepileptic effect has been documented in clinical practice. In addition, Dashputra et al. [27] assessed the combination of ketamine with antiepileptic medications to address the concern about utilizing ketamine as a general anesthetic agent in vulnerable patients. The findings revealed that ketamine amplified chemo-shock seizures, yet it granted protection against electroshock seizures. It is noteworthy that chemo-shock seizures are seizures that are provoked with chemical compounds like pentylenetetrazole, but electro-shock seizures are seizures that are elicited during procedures like ECT. Moreover, when ketamine was administered in combination with antiepileptic drugs, it exhibited a much stronger protective effect against electroshock seizures compared to using either drug alone. Interestingly, regarding the chemo-shock Seizures, ketamine exerted protection when combined with benzodiazepines (100 %) and antagonism with phenytoin and fosphenytoin (0 %) while no change was observed when combined with sodium valproate and phenobarbitone (20 and 30 %). It has been hypothesized that combination of ketamine with antiepileptic drugs prevents degeneration of thalamic neurons induced by focal cortical seizures but the exact mechanism of this confliction remains unknown.

Another study found that combining ketamine in combination with phenytoin and fosphenytoin might play a role in managing grand mal epilepsy [27].

In 1973, Ferrer-Allado et al. used cortical, thalamic, and limbic implants (which may trigger fits per se) to study the effect of ketamine in 9 patients with epilepsy [29]. They reported seizures associated with the combination of ketamine, thiopental, and nitrous oxide that was not observed with N2O or thiopental administration alone. These seizures were reported with intravenous doses of 0.5 mg/kg and 2 mg/kg, but not with 1 mg/kg. They concluded that the seizures experienced by patients were likely related to ketamine administration. They recommended using ketamine with caution or not at all in patients with epilepsy. Finally, two more recent cases showed ketamine to be implicated in new onset seizures [20,30]. Of note, both cases had the same circumstances; the patients were children, and ketamine was injected intramuscularly for sedation to repair a laceration!

One of these children was diagnosed with autism which has a high co-occurrence of epilepsy [31]. Moreover, the brain computed tomography of this child showed mild colpocephaly of the ventricles which is coincidental with epilepsy. The epilepsy (which was generalized tonic-clonic of 1-min duration) was only without any medications.

While both were case reports (the lowest level of evidence), mounting research has been showing the safety of ketamine for procedural sedation in the pediatric population (the same circumstances for the two case reports) [32–34] [32–34] [32–34]. But these studies were old and limited by inclusion of only 9 patients. However recently Ketamine treatment was associated with a decrease in seizure burden in patients with super-refractory status epilepticus (SRSE) [35].

Therefore, it is imperative to appreciate that there is no solid evidence that ketamine is likely to precipitate epilepsy even in epileptic patients.

3.2. Ketamine as an antiepileptic agent

Ketamine has recently been proposed as a third-line anti-epileptic drug for refractory and super refractory status epilepticus. This is contrary to earlier studies that propose a pro-epileptic role for ketamine. During seizures, the number and activity of GABA receptors steadily diminish, causing first- and second-line antiepileptic medications to lose effectiveness while ketamine exerts various actions on different pathways.

3.2.1. NMDA antagonism

Ketamine works, in part, by blocking glutamatergic transmission by antagonizing NMDA receptors [35]. Its pathway of action has made it an attractive option for the management of refractory status epilepticus [36]. Refractory epilepsy is a medical emergency that occurs when seizures persist despite treatment using first- and second-line antiepileptic medications [37]. By inhibiting NMDA receptors, ketamine modifies the excitatory glutamatergic signaling pathway, reducing neuronal hyperexcitability and epileptic frequency. Moreover, the antagonism of NMDA receptors by ketamine lowers excessive glutamate release, which contributes to the onset and propagation of seizures. This process enables reinstating the equilibrium between inhibitory and excitatory neurotransmission, hence reducing the likelihood of seizure occurrence [38].

3.2.2. GABA modulation

Ketamine interacts with the gamma-aminobutyric acid (GABA) system. GABA is the principal inhibitory neurotransmitter in the central nervous system and regulates neuronal excitability. Ketamine boosts GABAergic neurotransmission by enhancing the release of GABA and its binding to GABA-A receptors. This impact contributes further to the overall decrease in neuronal excitability and seizure sensitivity [39].

3.2.3. Anti-inflammatory effects

The pathogenesis of epilepsy involves inflammation, and inflammatory cytokines, and lowers the activation of central nervous system immune cells called microglia [40]. By reducing neuroinflammation, ketamine may slow the progression and development of epilepsy.

3.2.4. Neuroprotective effects

In multiple forms of neurological diseases, including epilepsy, ketamine exhibits neuroprotective properties as it decreases excitotoxicity by avoiding excessive glutamate release and associated neuronal damage [41]. In addition, ketamine can regulate neurotrophic factors, such as brain-derived neurotrophic factor (BDNF), which play key roles in synaptic plasticity, neuronal survival, and

neurogenesis [42].

3.3. Refractory (RSE) and super refractory status epilepticus (SRSE)

Recent literature has defined refractory status epilepticus (RSE) as either generalized or complex partial status epilepticus (SE) failing to respond to the first and second line of medications. In this regard, super refractory status epilepticus (SRSE) is a status epilepticus that remains unresponsive to medications despite 24 h of therapy with general anesthesia [43]. Both conditions are associated with severe morbidity and mortality [44].

Our search yielded three systematic reviews, one terminated randomized controlled trial, four retrospective analysis studies, along with case reports and series which showed that ketamine was generally, safe and effective (Table 1).

3.4. Adverse effects of ketamine

Two cases reported adverse events occurring after starting ketamine, however, none mentioned epilepsy. The first case developed abdominal compartment syndrome complicating ketamine infusion treatment for SRSE in a 74-years old man [45]. Another case was reported to develop cardiac arrhythmia following ketamine administration [46].

In 2022, Rosati et al. reported their experience from KETASER01, a multicenter randomized controlled trial that was terminated before the completion of data collection for the inability to recruit enough participants during the study period [47]. While no recommendation could be concluded from the study, it should be noted that two out of five children treated with ketamine had their seizures terminated after starting the medication.

Retrospective data analysis also confirmed the positive role ketamine plays in the treatment of RSE and SRSE in neonatal, pediatric, and adult populations [22,37,48–51].

Despite the lack of robust randomized trials, ketamine is generally preferred as a third-line medication for RSE and SRSE. In a recent guideline for the management of status epilepticus, Besha et., al listed ketamine as class 2a, which denotes the availability of systematic reviews [52]. In addition, a survey for Canadian physicians showed that 47.4 % of physicians working with patients with SE used ketamine for the treatment of RSE [53]. One concern about using ketamine in a clinical setting is that it does not lead to complete burst suppression, which might imply incomplete termination of seizure activity. A recent study by Fisch et al. found that burst suppression (in RSE in general) is clinically infrequent and had little (or even no) benefit in improving outcomes or stopping seizures [54]. In adult patients with RSE treated with IVAD, burst suppression with $\geq$50 % suppression proportion was achieved in every fifth patient and not associated with persistent seizure termination, in-hospital survival, or return to premorbid neurologic function.

3.5. Pro or antiepileptic?

Several studies in both humans and animals strongly suggested that ketamine possesses antiepileptic properties. While evidence supporting ketamine related efficacy in the treatment of seizures has many postulated mechanisms, the exact mechanisms behind its potential to provoke seizures is not fully understood [20].

In addition to the present evidence, which is not consistent, it is noteworthy that ketamine-induced seizures appear to occur in certain contexts, such as procedural sedation especially when ketamine was used as a single agent. Moreover, it seems that there is individual susceptibility which is not well-defined as genetic factors and alterations in the brain's excitability threshold [55]. Therefore, combining ketamine with propofol or benzodiazepines (both have antiepileptic characteristics) should decrease the incidence of epilepsy [56–58]. In addition, these combinations have showed better clinical efficiency than single drugs about sedation and safety profile [59,60].

As regard ketofol (ketamine combined with propofol), a large single-center case series showed that it was effective in control of super-refractory status epilepticus [61].

For benzodiazepines, the combination therapy of ketamine and midazolam in patients with refractory status epilepticus effectively suppressed the epileptic discharge with less hemodynamic side effects [62].

3.6. Limitations

Our comparison was limited by the limited availability of data on the probable epileptogenic effect of ketamine, we think that our study will draw more attention into reporting ketamine effect whether it is epileptogenic or anti-epileptic.

4. Conclusion

Existing research does not conclude definitively that ketamine is a pro-epileptic agent. However, in epileptic or susceptible patients undergoing procedural sedation, the results of this investigation recommended combining ketamine with a benzodiazepine agent or propofol. The combination therapy can enhance safety against provoking epilepsy and offers better outcome for sedation. Therefore, there is no good reason to deprive epileptic patients of the beneficial effects of ketamine. Future research is needed to fully elucidate the mechanisms of ketamine-induced seizures and identify individuals at higher risk.

CRediT authorship contribution statement

Islam Mohammad Shehata: Writing - review & editing, Writing - original draft, Supervision, Investigation, Conceptualization. **Neveen A. Kohaf:** Writing - review & editing, Writing - original draft. **Mohamed W. ElSayed:** Writing - original draft. **Kaveh Latifi:** Writing - review & editing. **Aya Moustafa Aboutaleb:** Writing - review & editing, Software, Methodology. **Alan David Kaye:** Supervision.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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