ISSN: 2583-5386
DOI: doi.org/10.51219/JIH/veronica-ruiz-vasconcelos/31

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Journal of Integrated Health

https://urfpublishers.com/journal/integrated-health

Vol: 3 & Iss: 1

Review Article

Ketamine and Neuroprotection in the Intensive Care Unit

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Citation: Verónica Ruiz Vasconcelos, et al. Ketamine and Neuroprotection in the Intensive Care Unit. *J Integrated Health* 2024;3(1):181-184. DOI: doi.org/10.51219/JIH/veronica-ruiz-vasconcelos/31

Received: 15 February, 2024; **Accepted:** 23 February, 2024; **Published:** 26 February, 2024

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A B S T R A C T

Ketamine is a phenylcyclinide derivative, which acts mainly as a non-competitive antagonist of N-methyl-D-aspartate (NMDA) receptors. It is a drug that serves as an anesthetic inducer, being very useful in patients with hemodynamic instability, since it inhibits the reuptake of catecholamines. In intensive therapy and in the neurocritical patient, ketamine can be used for the management of refractory and super-refractory status epilepticus, as well as for sedation management in patients with traumatic brain injury and as an adjuvant for sedation of the mechanically ventilated neurocritical patient.

1. Introduction

Ketamine is an anesthetic drug, which was first described in 1962 and was approvedfor clinical use until 1968. It is a drug that serves as an anesthetic inducer, being very useful in patients with hemodynamic instability, since it inhibits the reuptake of catecholamines, it is also considered a bronchodilator drug, so it can be very usefulin patients with asthma[1].

The use of ketamine in the neurocritical patient was limited because, in some studies, it increased intracranial pressure and intraocular pressure; however, this information has been refuted and is no longer valid[2].

Nowadays, ketamine is a drug with a very versatile pharmacokinetic and pharmacodynamic profile, allowing its use in multiple clinical scenarios, making thisdrug a very useful tool especially for the sedation of patients in intensive care. The present narrative review of the literature aims to summarize the main neuroprotectivecharacteristics of ketamine, as well as to mention the efficacy of this drug in its different applications in the neurocritical patient.

2. Pharmacological Properties of Ketamine

Ketamine is a phenylcyclinide derivative, which acts primarily as a non-competitive antagonist of N-methyl-D-aspartate (NMDA) receptors, its non-affinity for gamma-aminobutyric acid receptors in the central nervous system is well known. It is the only intravenous anesthetic drug with diverse properties, ranging from hypnotic, analgesic and amnesic[3].

It consists of two optical isomers or enantiomers, which are S (+)-ketamine hydrochloride and R (-) ketamine hydrochloride. The S (+) enantiomer has shown greater anesthetic and analgesic potency, as well as a lower tendency to agitation reactions. The use of S-ketamine has increased considerably worldwide since the S (+) enantiomer was shown to be up to 4 times more potent as an anesthetic and analgesic than the R (-) enantiomer[3].

Ketamine undergoes oxidative metabolism, primarily to norketamine by cytochrome P450 (CYP) 3A4 and CYP 2B6, which may be altered in conditions such as hepaticimpairment or drug-drug interactions. In the general population, the elimination half-life of ketamine is approximately 2-3 hours.

Once metabolized, via hepatic N- dealkylation, norketamine can be 33% as potent as the parent compound, which may prolong the clinical effect of ketamine. Ketamine is a lipophilic drug with limitedprotein binding, allowing wider distribution in the central nervous system.

The routes of administration of ketamine are very variable, it can be intravenous (IV),intramuscular (IM), rectal, intranasal or oral (O.V.), however, due to the extensive first-pass metabolism to which it undergoes, the bioavailability of the oral route is very poor. Ketamine has a very favorable pharmacokinetic profile in the context of intensive therapy, due to its rapid onset of action, as well as its clearance via cytochrome P450. Table 1 summarizes the main characteristics of ketamine, as wellas the dosage.

Table 1: Pharmacological characteristics and dosage of ketamine.

Properties	Values		
Start of action			
· *IM*	o 3-5 min		
· *IV*	o 30-40 sec		
· *IN*	o 10 min		
Duration of action			
· *IM*	o 12-25 min		
· *IV*	o 5-10 min		
· *IN*	o 60 min		
Bioavailability			
· *IM*	o 93%		
· *IN*	o 25-50%		
· *VO*	o 20-25%		
Dose	**IV**	**IM**	**IN**
Induction	0.5-2 mg/kg	3.5 mg/kg	mg/kg 0.25-4
Sedation	0.2-0.8 mg/kg	2-4 mg/kg	mg/kg 3-10

Currently there are multiple theories about the mechanism of action of ketamine. The main theory lies in the effect that ketamine induces in the CNS, this effect is produced through non-competitive antagonism in the N-methyl-D-aspartate (NMDA) receptors, as well as the interactions that it generates in other sites, as a partial agonist of mu-type opioid receptors in central and spinal sites and the interaction with noradrenaline, serotonin and muscarinic receptors.

The anesthetic, analgesic and neuroprotective effects of ketamine, as well as the dissociative state it produces, are generated by the inhibition of the activity of excitatory amino acids such as aspartate and glutamate in the brain. Due to the potent antagonism that ketamine produces on the NMDA subtype glutamate receptor, it prevents the entry of calcium into the cell, thus generating a blockage inthe production of nitric oxide, this from the Ca2+/calmodulin complex; resulting in an inhibition in the increase in the concentration of cGMP.

3. Use of Ketamine in the Neurocritical Patient

The use of ketamine in the neurocritical patient was limited, it was thought that it produced elevation of intracranial pressure, but it is certain that it produces cerebral vasoconstriction, increase in the metabolic consumption of oxygen and increase in the production of cerebrospinal fluid, therefore, it can elevate the intracranial pressure[4]. However, the studies that reported this effect on intracranial pressure were trials with few patients who were ventilating spontaneously and who, after ketamine administration, presented an increase in PaCO2, which could be the causeof the elevation in ICP. Currently, it has been demonstrated that the use of ketamine does not increase intracranial pressure in sedated and mechanically ventilated patients with severe traumatic brain injury[5].

Ketamine has been shown to have neuroprotective and even anti-inflammatory properties. This is why ketamine has become a drug of interest in multiple areas of medicine.

Specifically, in the intensive care unit and in the neurocritical patient, ketamine can be used for the management of refractory and super-refractory status epilepticus, as well as for sedation management in traumatic brain injury patients and as an adjuvant for sedation of the mechanically ventilated neurocritical patient[6].

4. Neuroprotective Effects of Ketamine

Ketamine inhibits NMDA receptor activation and excitotoxic injury signaling, reduces neuronal apoptosis, attenuates the systemic inflammatory response of injured tissues, and maintains cerebral perfusion pressure as a result of activation of the sympathetic nervous system[7].

The neuroprotective mechanism of ketamine is mainly based on the modulation of glutamate. It is known that ketamine exerts its neuroprotective effect, basically in twoways; 1. Presynaptic, inhibiting glutamate secretion and 2. Postsynaptic, acting as a competitive blocker of NMDA receptors, consequently, it prevents excitotoxic injury,avoiding both calcium entry into the cells, as well as the formation of nitric oxide andthe formation of free radicals[8].

5. Refractory and Super-Refractory Status Epilepticus

Refractory status epilepticus is defined as persistent seizures, which are resistant tofirst-line and second-line treatment, usually requiring deep sedation and continuouselectroencephalographic monitoring. Generally, anesthetic medications such aspropofol, midazolam or barbiturates are ideal for the management of refractory status epilepticus[9].

There is a status epilepticus called super refractory, which is defined as a persistent status epilepticus despite receiving treatment with anesthetics for more than 24 hours, generally these patients have a high morbi-mortality and are in intensive care units, under deep sedation, mainly with propofol or barbiturates[10].

The main theory on the use of ketamine for patients in refractory status epilepticus is based on the mechanism of action of ketamine, which has no effect on GABA receptors and targets different NMDA receptor pathways, offering a different therapeutic option.

In 2015, Fang et al. conducted a narrative review on the use of ketamine for the treatment of refractory and super-refractory status epilepticus, in this publication theysummarize a series of articles ranging from case reports to prospective studies where it is concluded that, in prolonged status epilepticus, the number and functionof GABA receptors decreases considerably, so that first and second line therapies tend to fail. Due to the above and considering that the number and activity of glutaminergic NMDA receptors tend to increase, ketamine is a therapeutic possibilityfor patients with refractory and super-refractory status epilepticus[11].

Based on the above and with the background of the efficacy of ketamine for the treatment of refractory and super-refractory

status epilepticus, a search for new evidence on the use of ketamine in this type of patients was performed. In summary,we found 4 studies, from 2015 to 2020, that discuss the efficacy of ketamine for themanagement of refractory and super-refractory status epilepticus, which are summarized in the following table[12-15].

Table 2: Summary of articles on ketamine in refractory and super-refractory status epilepticus.

Study	n	Type of study	Intervention	**Outcome**	**Result**
Alkhachroum, et al. 2020	68	Retrospective	Ketamine + midazolam	Complete cessation of seizures. >50% reduction in seizures	43 (63%) cessation of seizures 55 (81%) at least 50% seizure reduction in 24 hours.
Hofler, et al, 2016	42	Retrospective	Ketamine + propofol	Seizure control Mortality	Seizure control in 64%.
					Mortality rate of 45.2%.
Sabharwal, V, et al. 2015	67	Retrospective	Ketamine + propofol	Resolution of seizures Mortality	91% resolution of seizures. Mortality associated with anoxia 67%; Mortality in controlled patients 44%.
Koffman, et al, 2017	9	Case Report		To evaluate the incidence of arrhythmias due to the use of ketamine.	2 patients presented arrhythmias; 1 severe.

The 2020 study by Alkhachroum et al. showed that 80% of patients with refractory status epilepticus had a 50% decrease in seizures within 24 hours after the initiationof ketamine and 63% of patients had a cessation of seizures with the use of ketamine. In addition, a decrease in mortality was found in patients in whom seizuresceased following ketamine use[12].

Because of these antiepileptogenic results and the neuroprotective effects generated by ketamine, Fujikawa proposed the theory of early management of patients with status epilepticus with ketamine. However, no randomized studies have yet been conducted to demonstrate the efficacy of this theory[16].

6. Ketamine and Intracranial Pressure

[17]Ketamine maintains intracranial pressure unchanged or may even decrease it if associated with an increase in cerebral perfusion pressure. Moreover, it does not compromise cerebral auto-regulatory mechanisms or carbon dioxide vascular reactivity. It also has a neuroprotective effect by decreasing glutamate levels and inhibiting cortical depolarization[18].

To study the effect of ketamine on intracranial pressure, Zeiler et al. conducted a systematic review of the literature in 2014, looking for studies that evaluated the effect of ketamine on intracranial pressure in traumatic brain injury. The authors demonstrated that infused ketamine has the same effectiveness as opioid-based infusions in terms of sedation. In addition, they found that, infused ketamine does not lead to elevations or fluctuations of intracranial pressure, but increases cerebral perfusion pressure and decreases the use of vasopressors, compared to opioids[19].

Other relevant findings of this review were that ketamine administered in boluses decreases intracranial pressure, either from baseline or in episodes of intracranial hypertension, contrary to what was thought in previous years. Finally, it showed a favorable safety profile in this review, since there were very few complications associated with its administration[19].

Tofte Gregers and collaborators in 2020, conducted a review on the use of ketamineas an anesthetic for patients with acute traumatic brain injury, evaluated a total of 11clinical studies, with 334 patients, looking for the effects of ketamine on the central nervous system in patients with acute traumatic brain injury. The results concluded that there was no evidence to indicate that the use of ketamine in patients with acutetraumatic brain injury will generate a worsening of brain conditions, referring to intracranial pressure, cerebral perfusion pressure, hemodynamic alterations and mortality[20].

In conclusion, ketamine is a safe and effective sedative drug for the management ofsedation in patients with traumatic brain injury, without raising intracranial pressure.It is true that the evidence is not conclusive, however, it is also important to mentionthat there is no evidence that ketamine produces harm in this type of patients.

7. Ketamine as Adjuvant for Sedoanalgesia in IMV

There is little information on the use of ketamine as an adjuvant for sedation outside the operating room. Ketamine should be considered as a very good option for sedation analgesia of mechanically ventilated patients, due to its ability to reduce opioid requirements and avoid hemodynamic instability. In this narrative review, 3 articles were found that evaluate the efficacy of ketamine in different sedation contexts and despite not being studies specifically performed in neurocritical patients, the studies mentioned below include sedated patients with some neurological pathology.

Groetzinger et al, in 2018, analyzed the use of ketamine as an adjuvant in the sedation of critically ill patients who were mechanically ventilated, it was a retrospective study of 91 patients, in which ketamine was administered via infusion,with an average dose of 0.41 mg/kg/hour, for a mean of 14.7 days, accompanied byany other sedative medication, such as propofol or benzodiazepines. In conclusion, patients who received ketamine had a lower incidence of agitation[21].

Based on the theory that ketamine has both sedative and analgesic effects, attemptshave been made to demonstrate that ketamine infusions can reduce not only sedative doses but also opioid doses, under this idea Garber and colleagues conducted a retrospective study in two hospital centers. The primary objective was to evaluate the changes in sedation-analgesia in 24 hours after the initiation of ketamine. A total of 104 patients were analyzed, finding a 20% reduction in sedation-analgesic infusions within 24 hours after initiation of ketamine, with significantly lowerdoses of fentanyl and propofol. The population of this study is not solely neurocritical,but does include a total of 10 patients who were in neurological intensive care[22].

In another study by Jaeger et al, a sedation-analgesia scheme with either propofol, fentanyl, midazolam or dexmedetomdinine with ketamine as adjuvant was comparedagainst another group without ketamine. The primary endpoint was the percentage of Richmond agitation-sedation scale and secondary endpoints included percentage of pain, days of stay in the ICU, opioid and vasopressor consumption, as well as in-hospital mortality. In total, 172 patients were retrospectively analyzed (86 in each

group), with respect to the percentage of RASS, there was no statistically significant difference, i.e. ketamine did not prove useful in achieving an adequate level of sedation when used as an adjuvant. However, in the ketamine group, few patients required fentanyl infusions, received fewer days of benzodiazepines and above all less vasopressor support[23].

Ketamine may not have a better sedation profile than the rest of the sedatives, however, it is a drug that as an adjuvant to sedation can help reduce the consumption of opioids and thus the adverse events that these can generate in patients. Likewise, ketamine as an adjuvant in sedation-analgesia helps to reduce the doses of sedatives and vasopressors. Clinical studies are retrospective. Undoubtedly, prospective randomized trials are required to confirm these findings.

In the context of the COVID-19 pandemic, sedation and analgesia in these patients has become a topic of great importance. After explaining and knowing the efficacy of ketamine in different entities, it is valid to mention that ketamine can be an excellent option as an adjuvant for the sedation-analgesia of patients with COVID-19. It is known that there is functional deterioration induced by excessive doses of sedatives, as well as delirium and depression in this type of patients.

Ketamine as an adjuvant in the sedation-analgesia of these patients would help in several ways, first, by having a bronchodilator effect it can help patients with asthma and COVID-19, it also reduces the consumption of opioids and reduces sedative- induced delirium. Another reason for using ketamine is the antidepressant effect it has; patients with COVID-19 may have mood alterations even months after discharge. Ketamine has proven to be an excellent antidepressant drug that can undoubtedly benefit this type of patients[24].

8. Conclusions

Ketamine as an ant epileptogenic drug has a promising future and there is the idea of early use without having to wait for the patient to reach a super-refractory state. On the other hand, the neuroprotective properties of ketamine may be useful in different contexts such as patients with ischemic lesions or patients with traumatic brain injuries, preventing apoptosis and brain death. Little evidence currently existson this situation, but it seems to have a bright future.

In terms of sedation and analgesia, ketamine has both properties, therefore, it is anoption as an adjuvant in sedation-analgesia, reducing the consumption of both opioids and sedatives and ensuring good hemodynamic stability.

Despite more than 50 years of studies on ketamine in the neurocritical patient, the quantity and quality of studies is not the best. The vast majority of clinical evidence comes from retrospective and prospective studies with few patients, so it is difficult to give a solid conclusion. However, there is a trend in favor of ketamine, since it has not been shown to produce harm in these patients either. The next step will be to generate randomized, multicenter studies that will help to better support this theory.

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