Refractory and super-refractory status epilepticus and evidence for the use of ketamine: a scope review

Luis Espinosa, MD¹; Mario Gomez, MD²; Adrian Zamora, MD³; Daniel Molano-Franco, MD, MsC⁴

¹Department of Intensive Care, Hospital San José FUCS, Hospital El Cruce (Buenos Aires), Clinic Santa Bárbara-CAFAM, Bogotá, Colombia
²Department of Intensive Care, Hospital San José FUCS, CIMCA Research Group, Bogotá, Colombia
³Department of Neurology, Sleep Section, Fundación Santafé de Bogotá, Bogotá, Colombia
⁴Department of Intensive Care, Hospital San José FUCS, Cobos Medical Center Clinic, GRIBOS Research Group and CIMCA, Coordinator of Intensive Care Clinics CAFAM, Bogotá, Colombia

INTRODUCTION

The incidence of status epilepticus (SE) ranges from approximately 5 to 40 per 100,000, based on several population-based studies across the US [1,2], and the incidence of super-refractory status epilepticus (SRSE) is 0.7 per 100,000. The response to treatment, its evolution time and duration, and the need to use one or more antiseizure drugs define SE as refractory or super-refractory. Ketamine has been used in SE management since the 90s when an article describing its use in treating SE was published. Since then, at least 24 publications have reported the use of ketamine for the treatment of SE in both adult and pediatric patients. This scoping review seeks to synthesize information on the use of drugs in super-refractory SE, specifically ketamine. Twenty articles were chosen for the final document construction. Few studies have investigated the use of ketamine in refractory status epilepticus (RSE) and super-refractory status epilepticus (SRSE). Most of the information comes from retrospective case series studies, mostly with small sample sizes, and although the information is heterogeneous, it points to the efficacy of ketamine as a third-line drug in RSE and SRSE, in controlling seizures.

Keywords: Ketamine; Anticonvulsants; Epileptic status; Treatment; Diagnosis
patients presenting with SE, depending on the cause, with mortality approaching 50% [5].

Ketamine, a drug derived from phencyclidine, was synthesized in 1960 and reached peak popularity in the 1970s. In 1982 it was reported that it could have another possible mechanism of action by agonism of μ, δ, and γ opioid receptors [6]. Another possible mechanism of action is the inhibition of monoamine oxidase, which prolongs the half-lives of serotonin, dopamine, and norepinephrine [7,8]. In a study published in 2011, a decrease in the production of interleukin (IL)-6, IL-8, IL-10, and tumor necrosis factor-alpha was found in patients undergoing cardiopulmonary surgery who received ketamine, which gives it certain anti-inflammatory properties [9]. Another study in 2015 observed that it caused a decrease in calcium concentration at the cytosolic level in cardiac myocytes, and thus counteracted its effect in states of hypoxia, ischemia, oxidative stress, and hypertrophic cardiomyopathy [10]. Ketamine occurs in two forms: the S isomer, which is three times more active than its opposite, the R-enantiomer. The most widely used pharmacological presentation is a racemic mixture of both molecular forms [11-13]. Despite its widespread use as an anesthetic during surgical procedures, it was not until the 1990s that an article was published showing its use in treating SE [14,15].

Glutamate receptors (pharmacological targets of ketamine) are classified into two types: metabotropic receptors (mGluRs), which promote the activation of second messengers via the activation of transmembrane G proteins, and ionotropic receptors, which are coupled to an ion channel and allow the entry of various ions, mainly calcium [16,17] (Fig. 1). Ionotropic receptors are divided according to the affinity of their specific agonists; here, N-methyl-D-aspartate (NMDA) receptors belong to this family.

Excitotoxicity is characterized by neuronal death induced by the excessive release of glutamate and overactivation of its receptors [18]. This event is associated with various disease states of the central nervous system, including epilepsy, hypoxia, ischemia and trauma. This overstimulation increases intracellular calcium concentrations; promotes lipid peroxidation of the cytoplasmic membrane, endoplasmic reticulum, and mitochondria and causes cell death [19,20].

METHODS

This scoping review seeks to synthesize available information from different domains of drug use in SRSE, specifically ketamine. No specific questions were raised and the definitions and variables used in different publications on the use of ketamine in SE were explored. Two researchers searched for articles using keywords in the PubMed, Embase, SciELO, Bireme, Latindex, and Google Scholar databases, and medRxiv was explored for gray literature. The words that were used to construct the search strategy were "status epilepticus," "refractory," and "ketamine."

RESULTS

A search of seven bibliographic databases identified 38 articles related to the terms of interest published between 1990 and 2022. Articles in English or Spanish were selected based on their titles or abstracts. After filtering by content and relevance, 20 articles were selected for the final document construction (Fig. 2). The extraction results were synthesized and presented as a qualitative description of the information and synthesis in quantitative data tables.

Pharmacokinetic profiles of ketamine

Table 1 shows the main causes of SE, including head trauma, cerebrovascular disease, infections, tumors, autoimmune disorders, and hypoxic-ischemic encephalopathy. The etiology of SE and SRSE is particular and suggests that both conditions are more likely to develop due to acute neurological damage associated with a persistent inflammatory state, but not specifically with the presence of epilepsy, an underlying pathology.

To initiate the pharmacological treatment of SE, it is crucial to understand the mechanism by which seizures become refractory.
excitatory activity [24-27]. This is clinically reflected in rapidly progressive resistance to benzodiazepines [28]. In this scenario of impaired GABAergic activity and increased excitotoxicity, NMDA receptor antagonists, such as ketamine, become therapeutically relevant because they have a pathophysiological substrate that favors their effectiveness (Fig. 3).

Other events are believed to occur at the tissue and cellular levels and contribute to the development of RSE and SRSE. Among these events, there may be mitochondrial failure or insufficient [29] and activation of the inflammatory cascade [30,31], which make the blood-brain barrier vulnerable together [32,33]. In treating SE, the primary therapeutic objective is to rapidly control ictal activity to limit neuronal death mediated by excitotoxicity and reduce the systemic complications generated, with benzodiazepines considered the first-line treatment. Other anticonvulsants such as phenytoin, levetiracetam, and valproic acid are the most widely used second-line drugs [34,35].

Having explored the pathophysiological substrate for which a third-line drug with effects on neuronal excitatory activity, specifically on NMDA receptors, could play a leading role, it is time to study the potential role of ketamine. In a retrospective study published in 1996 by Walker et al. [14], a case of SE was reported in which ketamine was used as an anticonvulsant drug, demonstrating a favorable therapeutic response, and no noteworthy adverse effects related to its use were reported. Since then, there have been 20 publications on ketamine and SE: nine case reports, eight retrospective case series, and one observational (Table 2) [5,14,15,36-52].

**Usefulness of ketamine in RSE**

In the analysis of the obtained information, two questions arose that motivated this investigation. Is ketamine useful in the treatment of RSE? Although seizures at any given moment may have a certain degree of clinical subjectivity, the two parameters used in the publications to determine the effectiveness of ketamine in RSE were clinical and electroencephalographic cessation of epileptiform activity. Between case reports and case series, there are 265 patients. A systematic review conducted in 2014 [46] grouped 110 patients, and another conducted in 2018 grouped 289 patients [5]. Of the 19 case studies, 12 (63%) achieved complete seizure control, whereas in the remaining case studies, seizure control was partial (31%) or absent (5%).

**Table 2: Main causes of refractory and super-refractory status epilepticus**

<table>
<thead>
<tr>
<th>Cause of refractory and super-refractory status epilepticus</th>
</tr>
</thead>
<tbody>
<tr>
<td>Head trauma</td>
</tr>
<tr>
<td>Cerebrovascular accidents</td>
</tr>
<tr>
<td>Central nervous system infections</td>
</tr>
<tr>
<td>Intracranial tumors</td>
</tr>
<tr>
<td>Cortical dysplasia</td>
</tr>
<tr>
<td>Hypoxic-ischemic encephalopathy</td>
</tr>
<tr>
<td>Metabolic disorders</td>
</tr>
<tr>
<td>Autoimmune disorders</td>
</tr>
<tr>
<td>Poisoning (including withdrawal syndrome)</td>
</tr>
</tbody>
</table>

Although the molecular pathophysiology of SE is complex, it composes with some of the body’s “laws of homeostasis.” For example, seizures are perpetuated by an imbalance between excitatory and inhibitory mechanisms in neuronal tissues [21]. γ-Aminobutyric acid (GABA) is the primary inhibitory and Glutamate is the main excitatory neurotransmitter that mediates excitation by stimulating the NMDA receptor [22,23].

After several minutes of constant seizure activity, “receptor trafficking” appears. This is a phenomenon in which GABA receptors decrease through a process of “internalization,” generating a reduction in GABAergic activity. The number of glutaminergic receptors on the cell surface increases due to “externalization” from the cytosol to the cell membrane, producing increased neuronal...
NMDA receptors are mobilized towards the synaptic membrane from amino acids located in the Golgi apparatus and are assembled into receptors that are transported in endosomes towards the cell membrane. As a result of this trafficking, the number of functional NMDA receptors per synapse increases while the number of functional GABA receptors decreases [53].

Also likely to have a direct relationship with the administered dose, with reported doses being higher than 0.9 mg/kg/hr [45, 50,51].

A negative aspect that limits the benefit of ketamine in this clinical scenario is recurrence after its cessation. This recurrence appears in 10%–60% of cases in which seizures are successfully suppressed [50,52]. The recurrence of seizures when withdrawing ketamine treatment depends on multiple factors that are difficult to associate with each other, including the etiology of RSE, comorbidities, severity of the convulsive condition, medications used concomitantly or previously, and disorders of the internal environment. This disparity makes it difficult to establish a causal relationship between these two events.

- What is the pharmacodynamic profile of ketamine in RSE?

We will analyze the information found on the loading dose, maintenance dose, start time of the drug, duration of treatment, and its therapeutic and adverse effects.

In 70% of the studies, a loading dose of ketamine was administered at a rate of 0.5 to 5 mg/kg. The intravenous infusion doses ranged from 0.05 to 10.5 mg/kg/hr, and for patients who received the drug enterally, the doses ranged from 50 to 250 mg twice a day. Ketamine treatment was administered between the first 24 hours and 140 days after the diagnosis of RES. The duration of ketamine treatment ranged from 2 hours to 29 days. The electroencephalographic response to ketamine treatment, as determined by the burst-suppression phenomenon, was as rapid as 2 hours or as delayed as 28 days.

**Adverse effects of ketamine**

The reported adverse effects included transient arterial hypertension (one case), supraventricular tachyarrhythmia (two cases), cerebellar syndrome (one case), metabolic acidosis in co-administration with midazolam (one case), and cardiovascular collapse associated with metabolic acidosis (two cases) [5]. However, the heterogeneity in pharmacodynamic information found when using ketamine as a third-line drug in RSE [5] constitutes an unfavorable aspect in determining its therapeutic index and other aspects of its pharmacodynamics. Little information is available regarding the oral administration of the drug. Oral ketamine has been used to control chronic pain in patients with neuropathic pain, cancers of different types, trigeminal neuralgia, and phantom limbs, among other conditions. The analgesic effect is mainly based on NMDA receptor activity. Although the bioavailability of orally administered ketamine is only 16%, its major active metabolite, norketamine, retains its NMDA receptor-antagonistic properties and has less affinity for NMDA receptors.

Until now, it has not been possible to determine the appropriate

---

**Fig. 3.** Receptor trafficking theory. Seizures produce many physiological effects and biochemical changes in the brain; within minutes, the trafficking of receptors causes some key adaptations. (A) Arrangement of γ-aminobutyric acid (GABA) receptors under normal conditions. (B) After recurrent seizures, GABA receptors in the synaptic membrane undergo a process of internalization. These membrane proteins are directed to endosomes in the cytosol or to the Golgi apparatus, where they are recycled to the cellular membrane. (C) Arrangement of N-methyl-D-aspartate (NMDA) receptors under normal conditions. (D) In synapses, unlike GABA receptors, NMDA receptors are mobilized towards the synaptic membrane from amino acids located in the Golgi apparatus and are assembled into receptors that are transported in endosomes to the cell membrane. As a result of this trafficking, the number of functional NMDA receptors per synapse increases while the number of functional GABA receptors decreases [53].
Table 2. Studies to the use of ketamine in refractory status epilepticus

<table>
<thead>
<tr>
<th>Study</th>
<th>Year</th>
<th>Study design</th>
<th>Number</th>
<th>Medication administration way</th>
<th>Previous bolus</th>
<th>Treatment time</th>
<th>Therapeutic response</th>
<th>Side effect</th>
</tr>
</thead>
<tbody>
<tr>
<td>Walker et al.</td>
<td>1996</td>
<td>Case report</td>
<td>1</td>
<td>IV</td>
<td>NI</td>
<td>NI</td>
<td>Not improvement</td>
<td>None</td>
</tr>
<tr>
<td>Kofke et al.</td>
<td>1997</td>
<td>Case report</td>
<td>1</td>
<td>IV</td>
<td>Yes</td>
<td>2 hr</td>
<td>Partial improvement</td>
<td>Tachyphylaxis</td>
</tr>
<tr>
<td>Ubogu et al.</td>
<td>2003</td>
<td>Case report</td>
<td>1</td>
<td>IV</td>
<td>Yes</td>
<td>5 day</td>
<td>Improvement</td>
<td>Neurotoxicity, cerebellar syndrome</td>
</tr>
<tr>
<td>Robakis et al.</td>
<td>2006</td>
<td>Case report</td>
<td>1</td>
<td>IV</td>
<td>NI</td>
<td>7 day</td>
<td>Partial improvement</td>
<td>None</td>
</tr>
<tr>
<td>Prüss et al.</td>
<td>2008</td>
<td>Case report</td>
<td>1</td>
<td>IV</td>
<td>Yes</td>
<td>14 day</td>
<td>Improvement</td>
<td>SH transitory</td>
</tr>
<tr>
<td>Hsieh et al.</td>
<td>2010</td>
<td>Case report</td>
<td>1</td>
<td>IV</td>
<td>Yes</td>
<td>7 day</td>
<td>Improvement</td>
<td>None</td>
</tr>
<tr>
<td>Yeh et al.</td>
<td>2011</td>
<td>Case report</td>
<td>1</td>
<td>IV/PO</td>
<td>Yes</td>
<td>Undefined/PO</td>
<td>Improvement</td>
<td>None</td>
</tr>
<tr>
<td>Kramer</td>
<td>2012</td>
<td>Case report</td>
<td>1</td>
<td>IV</td>
<td>Yes</td>
<td>3 day</td>
<td>Improvement</td>
<td>None</td>
</tr>
<tr>
<td>Synowiec et al.</td>
<td>2013</td>
<td>Case series</td>
<td>11</td>
<td>IV</td>
<td>Yes</td>
<td>4 hr–28 day</td>
<td>Improvement</td>
<td>None</td>
</tr>
<tr>
<td>Zeiler et al.</td>
<td>2013</td>
<td>Case report</td>
<td>2</td>
<td>IV</td>
<td>NI</td>
<td>3 hr–12 day</td>
<td>Improvement</td>
<td>None</td>
</tr>
<tr>
<td>Gaspard et al.</td>
<td>2013</td>
<td>Case series</td>
<td>46</td>
<td>IV</td>
<td>Yes</td>
<td>6 hr–27 day</td>
<td>Partial improvement</td>
<td>SVT</td>
</tr>
<tr>
<td>Zeiler et al.</td>
<td>2014</td>
<td>Systematic review</td>
<td>110</td>
<td>IV/PO</td>
<td>Yes</td>
<td>2 hr–27 day</td>
<td>Partial improvement</td>
<td>NI</td>
</tr>
<tr>
<td>Shrestha et al.</td>
<td>2015</td>
<td>Case series</td>
<td>2</td>
<td>IV</td>
<td>Yes</td>
<td>2 hr–3 day</td>
<td>Improvement</td>
<td>None</td>
</tr>
<tr>
<td>Sabharwal et al.</td>
<td>2015</td>
<td>Case series</td>
<td>67</td>
<td>IV</td>
<td>NI</td>
<td>1–29 day</td>
<td>Partial improvement</td>
<td>None</td>
</tr>
<tr>
<td>Höfler et al.</td>
<td>2017</td>
<td>Case series</td>
<td>42</td>
<td>IV</td>
<td>Yes</td>
<td>4 day</td>
<td>Partial improvement</td>
<td>None</td>
</tr>
<tr>
<td>Pizzi et al.</td>
<td>2017</td>
<td>Case report</td>
<td>1</td>
<td>IV/PO</td>
<td>NI</td>
<td>5 day</td>
<td>Partial improvement</td>
<td>None</td>
</tr>
<tr>
<td>Golub et al.</td>
<td>2018</td>
<td>Systematic review</td>
<td>289</td>
<td>IV/PO</td>
<td>Yes</td>
<td>NI</td>
<td>Partial improvement</td>
<td>NI</td>
</tr>
<tr>
<td>Alkhachroum et al.</td>
<td>2020</td>
<td>Case series</td>
<td>68</td>
<td>IV</td>
<td>NI</td>
<td>1–4 day</td>
<td>Improvement</td>
<td>NI</td>
</tr>
<tr>
<td>Dericioglu et al.</td>
<td>2021</td>
<td>Case series</td>
<td>7</td>
<td>IV</td>
<td>Yes</td>
<td>3–24 day</td>
<td>Improvement</td>
<td>Liver injury</td>
</tr>
<tr>
<td>Caranzano et al.</td>
<td>2022</td>
<td>Observational</td>
<td>11</td>
<td>IV</td>
<td>NI</td>
<td>1–16 day</td>
<td>Improvement</td>
<td>NI</td>
</tr>
</tbody>
</table>

IV, Intravenous; NI, non-informed; SH, sudden hypertension; PO, per os; SVT, supraventricular tachycardia.

dosage because the therapeutic range is extensive and ranges between 45 and 1,000 mg/day. However, in patients treated with enteral ketamine, its effectiveness in seizure control appears to be maintained, thus constituting an alternative in cases where the intravenous route cannot be used [13,41]. Regarding adverse effects, it is not easy to establish the association between these and ketamine. Is not a first- or second-line drug, once treatment with this NMDA antagonist is initiated, it is difficult to assign any adverse reactions to ketamine in a critically ill, polymedicated patient with at least two centrally acting drugs. Additionally, the wide range of doses administered and treatment durations complicate the establishment of the causality of a clinical condition with a particular drug. However, several publications have reported sialorrhea, hepatotoxicity, cholestasis, cardiac arrhythmias, and metabolic acidosis related to ketamine use [37,39,45,53-55]. Although this drug is popular because it does not have hemodynamic depressant effects, this is probably due to the release of endogenous catecholamines, which increase peripheral vascular resistance and heart rate [56-58]. Paradoxically, some reports indicated that the effects of endogenous catecholamines on intracellular calcium currents could prolong cardiac action potential and have adverse inotropic effects [59-61]. In patients undergoing multimodal neurological monitoring, ketamine infusion did not generate harmful changes in intracranial pressure, and it was possible to reduce vasopressor requirements [50].

This particularity of the cardiovascular system may correlate with the cardiovascular collapse observed in two cases where ketamine was used [5]. Metabolic acidosis, which has also been reported in the treatment of RSE, has no clear cause. Some hypotheses suggest that hydrochloric acid, a diluent of midazolam (the first-line drug), can cause hyperchloremia, and thus contribute to acidosis, homeostatic imbalance, and cardiovascular collapse [5].

**DISCUSSION**

The main goals of RSE and SRSE treatment are to preserve cortical function and reduce morbidity and mortality related to neuronal damage caused by prolonged seizure activity. Cognitive, behavioral, and functional alterations have been reported at rates higher than 75% in patients with RSE and are clearly related to the duration of seizures [62,63]. Given the current knowledge about the biomolecular changes that occur in the neuronal membrane during prolonged seizures and the early onset of drug resistance to GABAergic drugs, there are clear reasons to consider the early initiation of ketamine treatment in RSE protocols [3-26,28-35,
The scant prominence of ketamine as a rescue treatment for RSE is attributable, in some way, to medical inexperience with the use of the drug in this context, the heterogeneity of the information available regarding its pharmacodynamic profile and side effects, and the lack of studies that include ketamine within their protocols. Although in most studies ketamine was not used in the initial hours of ER and was only used after various anticonvulsants, it was effective in controlling seizures when administered, usually within the first 12 hours [5]. However, there is currently insufficient scientific evidence to support the use of ketamine as a first-line drug or as a monotherapy in the management of RSE and SRSE.

It is reasonable to assume that there is fear and insecurity when using drugs with such disparate pharmacodynamic profiles. It is likely that, as has happened with other drugs, further studies will endorse its use, even more so in extreme clinical scenarios, such as supra-refractory status. For example, only after several years of intravenous lorazepam and diazepam could their toxicity be overcome, finding that it was due to propylene glycol, the excipient used in their pharmacological presentation, rather than this toxicity being inherent to these benzodiazepines. Accordingly, the statistical power of the studies we included was insufficient to relate the infusion of ketamine to a positive or negative impact on the mortality of these patients.

Few studies of report type and case series with small sample sizes and low statistical power, have examined the use of ketamine in RSE and SRSE. Despite the limited available evidence, the rapid efficacy of ketamine in the treatment of RSE and SRSE has been documented. This fact, in addition to the molecular and pathophysiological substrates that support the use of the drug, should encourage further research in this regard. One of the aspects to be clarified is the safety profile of ketamine and its pharmacological interactions with the other anticonvulsants used in RSE and SRSE treatment to elucidate the mechanisms of metabolic acidosis and other homeostatic alterations reported in the studies with ketamine and RSE.

CONCLUSIONS

The treatment of RSE and SRSE represents a therapeutic challenge because of their high mortality rates and poor neurological outcomes. Early initiation of anticonvulant therapy and its effectiveness are crucial aspects of patient prognosis. Several animal models have shown that, in persistent seizures, the cell membrane experiences a decrease in GABAergic receptors and an increase in the expression of excitatory receptors, including NMDA glutamatergic receptors.

There are few studies on the use of ketamine in RSE and SRSE, and most of the information comes from case reports, case series, and retrospective studies, mostly with small or unique samples. Although the information is heterogeneous, it suggests that ketamine, used as a third-line drug for RSE and SRSE, is effective in controlling seizures. In this sense, it would be a drug with pathophysiological endorsement for use since the current evidence is favorable, if limited. Despite this, the nature of adverse reactions reported with the use of ketamine varies, and its cardiovascular effects and changes in the internal environment seem to be predominant. Given the methodological limitations of most publications in this regard, information on neurological outcomes measured using the Glasgow Outcome Scale (and modified Rankin scales in patients with SE and SRSE who received ketamine is heterogeneous and inconclusive.

The lack of randomized prospective studies constitutes a significant limitation in recommending and including ketamine in the RSE and SRSE protocols. Additionally, based on the changes in the biochemistry of the neuronal membrane and its receptors that occur in RSE, the question arises as to whether anti-glutaminergic drugs should be started early or as third-line drugs for this pathology. Despite these limitations, ketamine appears to have a promising outlook for RSE and SRSE.

ARTICLE INFORMATION

Ethics statement

This article complies with the requirements of research and publication ethics biomedical and the World Medical Association’s Declaration of Helsinki.

Conflict of interest

No potential conflict of interest relevant to this article.

ORCID

Daniel Molano-Franco https://orcid.org/0000-0003-3015-1320

Author contributions

Conceptualization: LE, DMF. Data curation: LE. Formal analysis: LE, DMF. Investigation: all authors. Methodology: DMF. Project administration: LE, MG. Resources: DMF. Software: DMF. Supervision: MG. Validation: AZ, MG. Visualization: DMF. Writing–original draft: all authors. Writing–review & editing: AZ.
REFERENCES

1. Trinka E, Cock H, Hesdorffer D, Rossetti AO, Scheffer IE, Shin-
nar S, et al. A definition and classification of status epilepticus:
2. Brophy GM, Bell R, Claassen J, Alldredge B, Bleck TP; Glau-
ser T, et al. Guidelines for the evaluation and management of sta-
 tus epilepticus. Neurocrit Care 2012;17:3-23.
3. Hocker SE, Britton JW, Mandrekar JN, Wijdicks EF, Rab-
instein AA. Predictors of outcome in refractory status epilepticus.
JAMA Neurol 2013;70:72-7.
4. Mayer SA, Claassen J, Lokin J, Mendelsohn F, Dennis LJ, Fitz-
simmons BF. Refractory status epilepticus: frequency, risk fac-
5. Golub D, Yanai A, Darzi K, Papadopoulos J, Kaufman B. Poten-
tial consequences of high-dose infusion of ketamine for refrac-
tory status epilepticus: case reports and systematic literature re-
6. Finck AD, Ngai SH. Opiate receptor mediation of ketamine an-
8. Persson J. Ketamine in pain management. CNS Neurosci Ther 
flammatory cytokine response during and after cardiopulmo-
10. Luo AT, Cao ZZ, Xiang Y, Zhang S, Qian CP, Fu C, et al. Ket-
amine attenuates the Na+ dependent Ca2+ overload in rabbit ventricular myocytes in vitro by inhibiting late Na+ and L-type 
11. Lois F, De Kock M. Something new about ketamine for pediat-
en O, Brandner B, et al. Ketamine: use in anesthesia. CNS Neuro-
13. Chenge-Said J, Campeñacho-Asencio MÁ, Castellanos-Acuña MJ. 
14. Walker MC, Howard RS, Smith SJ, Miller DH, Shorvon SD, 
Hirsch NP. Diagnosis and treatment of status epilepticus on 
15. Höfler J, Trinka E. Intravenous ketamine in status epilepticus. 
16. López-Colomé AM, Somohano F. N-methyl-D-aspartate recep-
tors in the retina: 3-[(+-)-2-carboxypiperazin-4-yl]-pro-
pyl-1-phosphonic acid (CPP) binding studies. Neuropharma-
ology 1992;31:577-84.
17. Ozawa S, Kamiya H, Tszuki K. Glutamate receptors in the 
mammalian central nervous system. Prog Neurobiol 1998; 
54:581-618.
18. Olney JW. New insights and new issues in developmental neu-
19. Mattson MP, LaFerla FM, Chan SL, Leissring MA, Shelp PN, 
Geiger JD. Calcium signaling in the ER: its role in neuronal 
plasticity and neurodegenerative disorders. Trends Neurosci 
20. Flores-Soto ME, Chaparro-Huerta V, Escoto-Delgadillo M, 
Vázquez-Valls E, González-Castañeda RE, Beas-Zarate C. Struc-
ture and function of NMDA-type glutamate receptor subunits. 
21. Fountain NB, Lothman EW. Pathophysiology of status epileptic-
22. Fujikawa DG. The temporal evolution of neuronal damage from 
pilocarpine-induced status epilepticus. Brain Res 1996;725:11-
22.
23. Treiman DM, Meyers PD, Walton NY, Collins JF, Colling C, 
Rowan AJ, et al. A comparison of four treatments for general-
792-8.
24. Arancibia-Cárcamo IL, Kittler JT. Regulation of GABA(A) re-
ceptor membrane trafficking and synaptic localization. Pharma-
25. Smith KR, Kittler JT. The cell biology of synaptic inhibition in 
ulation of NMDA receptors increases glutamatergic exci-
27. Chen JW, Wasterlain CG. Status epilepticus: pathophysiology 
28. Kapur J, Macdonald RL. Rapid seizure-induced reduction of 
benzodiazepine and Zn2+ sensitivity of hippocampal dentate 
29. Cock HR, Tong X, Hargreaves IP, Heales SJ, Clark JB, Patalos 
PN, et al. Mitochondrial dysfunction associated with neuronal 
death following status epilepticus in rat. Epilepsy Res 2002; 
48:157-68.
30. Tan KY, Neligan A, Shorvon SD. The uncommon causes of sta-
59. Hatakeyama N, Yamazaki M, Shibuya N, Yamamura S, Momose...


