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CLINICAL COMMENTARY

Ketamine in adult super-refractory status epilepticus: Efficacy analysis on a prospective registry

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Background: Status epilepticus (SE) persisting despite two anti-seizures medications (ASM) and anesthetics is labeled super refractory (SRSE), correlating with important morbidity and mortality. Its treatment relies on expert opinions. Due to its pharmacological properties, ketamine (KET) has received increasing attention, but data are essentially retrospective.

Aims: To describe an unselected cohort of adults receiving KET for SRSE.

Methods: Analysis of a prospective registry of consecutive SE episodes, identifying SRSE patients receiving ketamine (KET). Comparison with recent adult series including more than 10 patients.

Results: Eleven patients received KET after a median of 4 days (range: 2–20); median dose was 5 mg/kg/h (range: 2.5–15). KET provided permanent SE control in three (27%). Previous series, using KET administration delays and doses similar to our cohort, report KET efficacy in 28–96% of cases.

Conclusions: We found a lower SE control rate than existing literature, whose data are, however, often retrospective, potentially selecting patients with less severe SE forms or responding to KET. This might explain outcome differences, as KET administration modalities were comparable with our cohort. Since randomized controlled studies are lacking on this subject, the analysis of this prospective, unselected cohort, if confirmed, suggests a current overestimation of KET efficacy in SRSE.

KEYWORDS
coma, general anesthetic, ketamine, outcome, prognosis, refractory status epilepticus, therapeutic, treatment

1 | INTRODUCTION

Status epilepticus (SE) represents a neurological emergency implying significant morbidity and mortality. If persisting despite two adequate treatment lines, it is defined as refractory (RSE), with[1] or without[2] need of anesthetics, while if continuing for 24 h despite general anesthesia as super refractory (SRSE).[1] These entities bear an increasing mortality risk, up to 40%, depending on underlying patient characteristics, SE etiologies, history of seizures, and treatment regimen.[3-5] High mortality has been reported when SE results from acute brain injury, such as stroke, infection,[6] or inflammatory conditions,[7] and severe, progressive entities, such as malignant brain tumors.

In animal models, ongoing SE induce internalization of postsynaptic gamma-amino-butyric-acid ($GABA_A$) receptors,[8] which could explain efficacy loss of benzodiazepines, while N-methyl-D-aspartate (NMDA) receptors are increased at cells surface.[8] Ketamine (KET), an NMDA antagonist, has shown in animal SE models promising findings.[9] In humans, the evidence of KET efficacy still relies on case reports and retrospective series with, to

our knowledge, only one large retrospective series of consecutive patients.[10] Randomized controlled clinical trials would be needed; however, considering the rarity of the condition, they are difficult to conduct. Therefore, further prospectively collected cohort assessments may offer a valuable alternative way to address the role of KET in SRSE treatment.

Our aim is to describe efficacy of KET in as unselected prospective SE population and compare it with previous literature.

2 | METHODS

We identified SRSE episodes receiving KET in our prospective registry (approved by our ethics commission) of consecutive adults treated for SE in our hospital between April 2006 and July 2021. Demographics, previous seizure history, etiology, worst SE semiology, Status Epilepticus Severity Score (STESS),[11] treatment regimens preceding and associated with KET, SE duration, SE control (clinical, electroencephalographical) during KET administration, SE control within 24 h following KET weaning, and outcome were prospectively collected, as previously described.[2] SE is consistently defined in the registry as continuous or intermittent seizures >5 min, implying EEG confirmation for non-convulsive semiology; SE following anoxic brain injury is not included. RSE is prospectively identified if at least two treatment lines (including benzodiazepines, but allowing also two ASM) were given beforehand with persisting SE. SRSE was identified for the present study by the persistent need of anesthetics drugs after 24 h; for the latter, patients' clinical information and EEG reports were screened. Our institution does not foresee a fixed treatment protocol for SRSE; this is at the discretion of the

TABLE 1 Patients' description

Patient #	Age	Gender	SE type	Etiology	Previous seizures	STESS	Other TT before KET
1	20	F	NCSE in coma	NORSE/FIRES	No	3	PRO, THP
2	25	F	GCTC	Anti-NMDA receptor encéphalitis	Yes	2	THP, MDZ, PRO, (steroids)
3	29	M	NCSE in coma	NORSE/FIRES	No	3	CLZ, VPA, MDZ, PRO, LEV, LCM
4	39	F	NCSE in coma	ASM Withdrawal	Yes	2	MDZ, CLZ, PRO, VPA
5	76	M	Partial Complex	HSD and stroke	No	3	LEV, VPA, LCM, PRO, MDZ
6	78	M	NCSE in coma	Viral encéphalitis (FSME)	No	6	LEV, CLZ, VPA, PRO, MDZ, LCM
7	46	M	NCSE in coma	NORSE/FIRES	No	3	CLZ, LEV, LCM, VPA, PRO, MDZ, PHT, THP, PGB, PB
8	54	F	NCSE in coma	Cerebral abscess	No	3	CLZ, LEV, LCM, VPA, PRO, MDZ, PER, PHT
9	72	M	NCSE in coma	Bacterial meningo-encéphalitis	No	5	LEV, CLZ, LZP, PRO, VPA
10	60	F	Partial Complex	Hyperglycémia and hémorrhage	No	2	MDZ, LEV, PRO, VPA, PHT
11	25	M	NCSE in coma	NORSE/FIRES	No	4	CLZ, PRO, LEV, LCM, PHT

Abbreviations: ASM, anti-seizures medication; CBZ, carbamazepine; CLZ, clonazepam; ECT, electroconvulsive therapy; F, female; FIRES, Febrile infection-related epilepsy syndrome; GCTC, generalized convulsive tonic-clonic seizures; HSD, sub-dural hematoma; KET, ketamine; LCM, lacosamide; LEV, levetiracetam; LZP, lorazepam; MDZ, midazolam; NCSE, non-convulsive status epilepticus in coma; NORSE, new-onset refractory status epilepticus; PB, phénobarbital; PER, perampanel; PGB, pregabaline; PHT, phenytoin; PRIS, propofol-related infusion syndrome; PRO, propofol; SE, status epilepticus; STESS, Status epilepticus severity score; THP, thiopental; TPM, topiramate; TT, treatment; VPA, valproate.

treating physician, counseled by the senior authors AR or JN. KET is routinely administered together with a GABA-ergic agent (propofol or midazolam).

We searched the Pubmed database (MeSH terms "ketamine AND status epilepticus" on 16.08.2021) and screened the abstracts for case series of at least 10 patients published after January 2011. We then screened full-text articles for eligibility, and the bibliography of the selected publications for missed articles. We included only publications in English. We did not analyze patients with SRSE following an anoxic brain injury and pediatric studies; in papers reporting miscellaneous populations, we only considered data from adults.

Statistics were computed using Microsoft® Excel® (©2016 Microsoft corporation, Redmond, Washington, United States of America). Normally distributed variables were described using means and standard deviation (±SD), otherwise using medians and range.

Due to the retrospective, purely observational nature of our study and analyses conducted on anonymous data, informed consensus is waived in accordance with the Swiss law.

3 | RESULTS

3.1 | Study cohort

Among 1358 SE episodes in our registry, we identified 42 SRSE, corresponding to 3.1%. Eleven (26%; 5 women) of them were treated using KET and are presented in Table 1. Mean age (±SD) was

KET							
Delay since SE start (d)	Maximum dose (mg/kg/h)	TT duration (d)	Other TT during KET	SE control under KET	SE control after KET weaning	SE duration (d)	Outcome at discharge
9	15	11	PRO, CLZ, PHT, LEV, TPM, steroids	Yes	No	96	New handicap
16	11	5	MDZ, CBZ, TPM, PGB, PB	Yes	No	77	Restitutio
4	10	4	MDZ, VPA, LCM	No	No	39	New handicap
3	5	1	MDZ, VPA, LEV	No	No	4	Death (Cerebral edema)
3	5	1	MDZ, VPA, LCM	Yes	No	11	New handicap
4	6	1	MDZ, LCM, VPA, PB	Yes	No	8	New handicap
20	5	3	MDZ, PHT, PB, PGB	Yes	Yes	20	New handicap
6	2.5	1	MDZ, LEV, LCM, PHT	No	No	28	New handicap
4	5	1	MDZ, LEV, LCM, VPA	Yes	Yes	5	Death (infectious encephalopathy)
2	5	2	PRO, VPA, PHT	Yes	Yes	3	Death (Toxic Arythmia, PRIS or PHT)
3	5	16	MDZ, LEV, VPA, THP, BRV, PB, Mozart KV448, ECT Solumedrol, Anakinra, Plasmapheresis, Cyclophosphamide, IVIG	No	No	26	Death in SE (Multiorgan failure)

TABLE 2 Previous series describing adults treated with KET for SE

Study	Year	Nb. of pts.	Latence to KET (days)	Dose (mg/kg/h)	Treatment duration (days)	Control during KET	Control after KET weaning	Mortality
Gaspard et al [12]	2013	46	26.5 (1 h–10 months) Median (range)	2.75 (0.05–10) Median (range)	9 (6 h–27 days) Median (range)	23/60 (38.3%)[c]	15/53 (28.3%)[b]	26/46 (56.5%)[a]
Synowiec et al [13]	2013	11	5 (1–11) Median (range)	1.2 (±0.6) Mean (±SD)	9.8 (±8.9) Mean (±SD)	11/11 (100%)	7/11 (64%)	2/11 (18.2%)
Basha et al [14]	2015	10	5.8 (±3.9) Mean (±SD)	3. (±1.6) Mean (±SD)	3.8 (2–26) Median (range)	4/10 (40%)	2/10 (20%)	2/10 (20.0%)
Sabharwal et al [15]	2015	54[b]	1–2 Range[d]	1.5–10.5 Range[d]	3.6 (1–28) Mean (range)[d]	NA	52/54 (96.3%)[b]	17/54 (31.5%)[b]
Höfler et al [16]	2016	28	3 (2–7)[a] Median (IQR)	2.4 (1.5–3.0)[a] Median (IQR)	4 (2–7)[a] Median (IQR)	18/28 (64.3%)	18/28 (64.3%)	14/28 (50%)
Alkhachroum et al[10]	2020	50	2 (1–4.5)[a] Median (IQR)	2.2 (±1.8)[a] Mean (±SD)	2 (1–4)[a] Median (IQR)	34 (68%)[a]	44/68 (65%)[a]	31/68 (45.6%)[a]
Current study	2021	11	4 (2–20) Median (range)	5 (2.5–15) Median (range)	2 (1–16) Median (range)	7/11 (63.7%)	3/11 (27.3%)	4/11 (36.4%)

Abbreviations: KET, ketamine; IQR, interquartile range; SD, standard deviation.

[a] Including post-anoxic encephalopathy.

[b] Including children.

[c] Including children and post-anoxic encephalopathy

[d] Reported as such.

48 ± 22 years. Only two patients had previous seizures, and the median STESS at presentation was 3 (range 2–6).

The median delay of KET administration since SE start was 4 days (range 2–20); median KET treatment duration was 2 days (range 1–16); and median KET dose was 5 mg/kg/h (range 2.5–15). SRSE control during KET administration occurred in 7/11 patients (63.6%), but only 3/11 (27.3%) patients had no relapse after its weaning (at discharge, two died, one had a new disability). Median SE duration was 20 days (range 3–96). At discharge, one patient (9.1%) had a complete recovery, 6 (54.5%) had a new handicap, and 4 (36.3%) died (one in SE).

Of the subgroup of 8 patients receiving KET within in the first SRSE week, at a dose ranging from 2.5 to 10 mg/kg/h, 4 achieved SRSE control during KET administration, this was maintained after weaning in two. Both, however, died after SRSE resolution (progression of a bacterial meningitis, cardiac arrhythmia).

3.2 | Literature search

This yielded 138 results: There were 5 retrospective series with at least 10 patients[12-16] and one large retrospective series of consecutive patients.[10] The six studies' details are presented in Table 2. If not specified otherwise, presented data correspond only to adults without post-anoxic encephalopathy, this patients selection accounts for differences between this series and previously published data.

When considering the 6 studies, the median control of SRSE persisting after KET weaning was 64.2% (range 28.3–96.3%), and the median mortality was 38.6% (range 18.2–50%).

4 | DISCUSSION

In our registry, KET was used in about one quarter of SRSE, allowing in less than half SE control during KET administration, and a sustained control in only one third of them, despite a globally early administration and the high doses used. Outcome at discharge of the three patients controlled by KET was unfavorable (two deaths due to underlying conditions, one new handicap).

SE etiologies of our patients underline the severity of our population, with four presenting Febrile infection-related epilepsy syndrome (FIRES) / new-onset refractory status epilepticus (NORSE), a condition burdened with very high mortality and long term morbidity,[7] as well as 3 others patients with infection-related causes.

Previously published adult series are mostly based on retrospective data ascertainment, which can suggest inclusion bias. As compared to the present cohort (Table 2), KET allowed SRSE control during its administration in a similar proportion, while persistent control was obtained more frequently. Additionally, the 64% proportion of SRSE control reported in a recent systematic review, including children,[17] is much higher than our proportion of 27%. Inclusion of patients with RSE (instead of SRSE), which are more easily controlled,[3] is probably at least partially responsible for better reported outcomes in four previous studies,[12-14,16] as well as the likely selection bias of retrospective assessments (possibly overestimating KET efficacy).

Previous data suggested increased KET efficacy in SRSE particularly when introduced within the first week and at doses >0.9 mg/kg/h.[12] Our study does not confirm those findings: The subgroup of eight patients receiving KET during the first week of disease, all with a dose higher of 1 mg/kg/h (the median highest doses compared to previous literature), does not show a better SRSE control.

Of note, in the largest study,[15] reporting an intriguing high proportion of permanent SRSE control (much higher than in other series), KET was initiated with propofol 24 h after SE onset, or even as first anesthetic in "most patients," thus including subjects with RSE. Moreover, SE control was not clearly defined, and no data on recurrence were provided. Similarly, a recent retrospective series of consecutive patients[10] defined SRSE as a SE persisting despite anesthetics administration, not mentioning a minimum time lapse. KET was given within 0.4–1 days from the beginning of midazolam, thus also likely including RSE patients. Therefore, our strict inclusion of patients with SRSE probably concentrated on episodes with more severe disease, but reflecting recent recommendations of KET use (which is not advocated as first-line anesthetic).[18] Also, while our patients' STESS was globally high, reflecting high risk of unfavorable prognosis, other studies do not consistently report a score for comparison.

Limitations of our study include the small sample size and the absence of a fixed protocol of SRSE treatment, which is reflected by variability of the delay of KET treatment start, its duration, and doses. Also, KET could have been given in particularly refractory patients. We do not have specific data regarding tolerability. Ketamine is a racemic mixture composed of the same amount of (R)-KET and (S)-KET (esketamine). The pharmacokinetic and pharmacodynamics property of esketamine make it a more potent analgesic agent, with faster clearance; it has been shown to have a good safety profile in RSE and SRSE, however, without formal proof of higher efficacy than KET.[16] In our institution, only the racemic mixture is available and was used in all patients. Finally, as in virtually every other similar assessment lacking randomization, the precise role of KET is challenged with a residual uncertainty given the high number of concomitant treatments.

Ideally, a randomized control clinical trial would be the best option to assess KET efficacy in this clinical context. However, a recent attempt in adults (ClinicalTrials.gov Identifier: NCT03115489) was withdrawn following low recruitment (not published), and another pediatric trial is currently terminated apparently for futility (ClinicalTrials.gov Identifier: NCT02431663, not published). Awaiting further attempts, multi-centric, prospective registries could provide highly valuable information, avoiding inclusion bias.

5 | CONCLUSION

The present data without obvious selection bias suggest that KET, while possibly useful in some patients, does not offer a sustained

control of SE in most SRSE episodes, even when administered within the first week of treatment at relatively high dose.

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CONFLICT OF INTEREST

The authors do not report any conflict of interest.

PEER REVIEW

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DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

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