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Intravenous ketamine for the treatment of refractory status epilepticus: a retrospective multi-center study

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Summary

Purpose—To examine patterns of use, efficacy and safety of intravenous ketamine for the treatment of refractory status epilepticus (RSE).

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Methods—Multicenter retrospective review of medical records and EEG reports in ten academic medical centers in North America and Europe, including 58 subjects, representing 60 episodes of RSE were identified between 1999 and 2012. Seven episodes occurred after anoxic brain injury.

Key findings—Permanent control of RSE was achieved in 57% (34/60) of episodes. Ketamine was felt to have contributed to permanent control ("possible" or "likely" responses) in 32% (19/60) including seven (12%) in which ketamine was the last drug added (likely responses). Four of the seven likely responses, but none of the 12 possible ones, occurred in patients with post-anoxic brain injury. No likely responses were observed when infusion rates were lower than 0.9mg/kg/h; when ketamine was introduced at least eight days after SE onset; or after failure of seven or more drugs. Ketamine was discontinued due to possible adverse events in five patients. Complications were mostly attributed to concurrent drugs, especially other anesthetics. Mortality rate was 43% (26/60), but was lower when SE was controlled within 24h of ketamine initiation (16% vs. 56%, p=0.0047).

Significance—Ketamine appears to be a relatively effective and safe drug for the treatment of RSE. This retrospective series provides preliminary data on effective dose and appropriate time of intervention to aid in the design of a prospective trial to further define the role of ketamine in the treatment of RSE.

Keywords

Ketamine; treatment; refractory status epilepticus; anesthetics; antiepileptic drugs

Introduction

Refractory status epilepticus (RSE) is defined as failure to respond to appropriate doses of two antiepileptic drugs.(Brophy et al. 2012) The treatment of RSE frequently requires anesthetic drugs, which can be associated with lethal complications. Prolonged seizures are accompanied by a decline in sensitivity to gamma-aminobutyric acid (GABA) agonists (Goodkin and Kapur 2009) but not to N-methyl-D-aspartate (NMDA) antagonists.(Mazarati and Wasterlain 1999) Since ketamine is an NMDA antagonist, and not associated with cardiorespiratory depression, (Hijazi et al. 2003) it is an attractive option for the treatment of RSE. Animal data suggest that ketamine may be an option for the treatment of prolonged status epilepticus.(Borris etal., 2000) Based on this and other animal studies, in the last several years ketamine has been used for the treatment of RSE in humans but most published data come from case reports or small series. (Kramer 2012; Rosati et al. 2012; Walker et al., 1995; Ubogu et al. 2003; Pruss and Holtkamp 2008; Kofke et al. 1997; Hsieh et al. 2010; Sheth and Gidal 1998; Synowiec et al. 2013)

The purpose of this study was to describe the experience with intravenous (IV) ketamine in the treatment of RSE across centers in North America and Europe.

Methods

The study was approved by the Institutional Review Board of each center. Cases of RSE treated with IV ketamine between 1999 and 2012 were retrospectively identified (Table e-1). Refractory SE was defined as failure of at least two anticonvulsant medications. Pharmacy records, electroencephalography (EEG) reports and intensive care unit (ICU) databases were reviewed. Methods of identification were specific to each institution in order to minimize recollection bias.

Data were collected using a standardized datasheet and all variables were available for all episodes except loading dose (available in 45/60), maximum infusion rate (54/60) and

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functional outcome (58/60). Outcome was measured at discharge using the modified Rankin Scale (mRS) for adults, and mortality and increase in dependency for children. Anesthetic drugs included propofol, midazolam, pentobarbital and thiopental.

"Likely response" to ketamine was defined as permanent control of SE within 24h of initiation if ketamine was the last drug added. "*Possible* response" was defined as permanent control of SE within 24h of initiation when ketamine was not the last drug added. *Permanent* control was defined as no recurrence of SE during the same ICU stay. Control of SE was defined as cessation of clinical and electrographic ictal manifestations as ascertained by continuous video-EEG monitoring (59 cases) or clinical evaluation and intermittent EEG (1 case of status epilepticus of infantile spasms). Adverse events were attributed to ketamine if they occurred after the initiation of ketamine and if they lead to a lowering of the dose or discontinuation.

We used Fisher Exact, Mann-Whitney, Kruskall-Wallis and Cochrane-Armitage tests, and multivariable stepwise logistic regression models, as appropriate.

Results

We identified 60 episodes of RSE treated with IV ketamine in 46 adults and 12 children (Table 1). More than half of the subjects had new-onset RSE of unknown etiology (sometimes referred to as NORSE), which was most often attributed to encephalitis with lack of a known causative organism or anti-neuronal antibody.

Ketamine was introduced after a median of nine days of SE (range: 0–122). We found wide variability in how it was administered. Common features included use of a loading dose (median: 1.5mg/kg; maximum: 5mg/kg) followed by continuous infusion (median: 2.75 mg/kg/h; maximum: 10 mg/kg/h). Ketamine was always part of a multi-drug regimen that ranged from two to 12 concurrent medications (Table e-2). The duration of infusion varied from six hours to 27 days.

Ketamine was likely responsible for control of SE in 12% of cases (7/60), and possibly responsible in an additional 20% (12/60; Table 2). SE was transiently controlled by ketamine in eight cases (13%). Likely response was not observed when infusion rates were lower than 0.9mg/kg/h; ketamine was introduced at least eight days after SE onset; or after failure of seven or more drugs. When given as the fourth line drug, likely and possible responses were observed in 4/10 and 2/10 cases, respectively. There were no specific drug combinations that improved response to ketamine. Further, we were not able to analyze the effect of ketamine on the used dose of concurrent benzodiazepines. Only the number of previously failed drugs was significantly associated with ketamine response (Table 2). As four likely (but none of the 12 possible responses) occurred in post-anoxic cases, we re-analyzed non-anoxic cases separately and found similar results. (Table e-3).

Ultimately, 34 episodes (57%) of status epilepticus were controlled. The overall mortality rate was 45% (26/60). Younger age and response to ketamine were associated with lower mortality in a stepwise multivariable logistic regression analysis (Table 3). Dose and duration of exposure to ketamine were not related to mortality. Among survivors, most had a poor functional status at discharge: only 2/46 (4%) adults had good outcome (mRS<=2) and one of 12 children returned to their baseline status. There was no difference in functional outcome in survivors whether they responded to ketamine or not.

Most patients were mechanically ventilated (56/60) and treated with vasopressors (52/60) prior to ketamine. Vasopressors were decreased in six patients but increased in 21 after initiation of ketamine. One third of patients developed complications while receiving

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ketamine, most commonly sepsis, shock, organ failure and pneumonia (Table e-4). We found no relationship between these complications and the dose or duration of exposure to ketamine but complications were higher when more than one other anesthetic drugs was used concurrently (Table 4).

Ketamine was discontinued in four cases (7%) due to suspected treatment-related adverse events. One patient developed a syndrome similar to the propofol-related infusion syndrome after 4 days of high dose ketamine (4.5mg/kg/h) and midazolam (2.5mg/kg/h), but no recent propofol use, and he recovered. Two patients developed supraventricular tachycardia that resolved after ketamine discontinuation. One other required the administration of amiodarone for atrial fibrillation. Additionally, ketamine was discontinued in one patient due to a probable adverse event that could not be reliably identified.

Intracranial pressure (ICP) monitoring was available during ketamine administration in seven cases. Two patients with cerebral edema from anoxic injury required osmotic therapy while on ketamine. Three patients were documented to have increased ICP prior to ketamine infusion but did not experience any worsening.

Discussion

We provide retrospective, multicenter data on the use of IV ketamine for the management of RSE. Our case series suggests that ketamine may be efficacious and relatively safe in sedated and ventilated children and adults.

The study population was a highly selected group of patients with prolonged refractory SE, as evidenced by the median number of failed drug trials before ketamine was administered (six drugs) and the median latency from onset of SE to ketamine administration (nine days). Thus, it is not surprising that 90% of cases were secondary to an acute brain injury or belonged to the category of new-onset refractory status epilepticus of unknown etiology (NORSE), which is usually attributed to encephalitis with lack of a known causative organism or anti-neuronal antibody and is associated with a relatively poor prognosis. (Mayer et al. 2002; Holtkamp et al., 2005; Holtkamp, et al. 2005; Costello et al., 2009)

The information regarding the therapeutic dosage or use of ketamine for the management of status epilepticus is scarce. Doses as high as 7.5 mg/kg/h used for up to 14 days have been described as safe.(Kramer 2012; Rosati et al. 2012) In our series, administration of doses up to 10 mg/kg/h for as many as 27 days was not associated with increased complications or mortality compared to patients receiving lower doses and shorter duration of exposure. Most importantly, all likely responses (permanent cessation of SE within 24h of ketamine initiation) occurred at doses of at least 0.9 mg/kg/h.

Permanent control of SE was likely or possibly attributed to ketamine in 32% (19/60) of episodes, and transient control in an additional 13% (8/60). Response rate was highest when ketamine was introduced “early”. When used as a third or fourth-line agent, ketamine was deemed responsible for control in 60% (6/10) of episodes of SE. Likely responses to ketamine were not reported when this drug was introduced more than one week after onset of SE or after the failure of seven or more drugs, although possible responses were seen. Available guidelines support the role of general anesthesia as the standard therapeutic approach to RSE despite the fact that most available evidence comes from uncontrolled case series. A systematic review of these series reports the efficacy (ability to control RSE without breakthrough seizures) to be 42%, 66% and 60% respectively for midazolam, propofol and barbiturates.(Claassen et al. 2002) A recent prospective trial comparing propofol to barbiturates was interrupted due to poor enrollment after 24 patients were enrolled.(Rossetti et al. 2011) Efficacy of propofol and barbiturates was 43% and 22%,

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respectively. In the majority of published cases, anesthetics were used as a third or fourth-line agent. Therefore, the efficacy of ketamine in our series is similar to other anesthetic agents, although lower than previous ketamine case series that reported an efficacy (permanent control of SE) of 63%(Synowiec et al. 2013) and72%.(Rosati et al. 2012) In these two series however, the majority of cases occurred in the setting of chronic epilepsy. This etiology carries a good prognostic factor compared to NORSE and acute brain injury, which accounted for the majority of cases in our series.

Consistent with previous reports, we identified few adverse events leading to the discontinuation of ketamine (Kramer 2012; Rosati et al. 2012; Synowiec et al. 2013) and most of them were related to the use of concurrent anesthetics and not to dose or duration of ketamine. One incident of severe acidosis with co-administration of high doses of ketamine and midazolam was life-threatening, a complication that has been reported only once for each drug.(Roervik and Stovner 1974; Federman et al., 2009) Apart from two patients with cerebral edema secondary to anoxic injury, no other patients were documented to have changes in intracranial pressure. This confirms that ketamine does not significantly raise ICP in ventilated patients.(Mayberg et al. 1995) Overall, the incidence of adverse events and mortality rate in our series is similar to other series of RSE. (Novy et al., 2010; Hocker et al. 2012) We found that mortality was lower in subjects who responded to ketamine but this may reflect lower severity of these episodes.

Data from animal models regarding the potential neurotoxicity of ketamine are controversial, as both neuronal apoptosis and neuroprotection have been reported. (Green and Coté 2009) Human data are limited to a single case of SE with a prolonged refractory course.(Ubogu et al. 2003) Given the severity and duration of most cases in our series and the confounding presence of acute brain injury and co-morbidities in many of our patients, we are unable to address this question, which should however be studied in any prospective trial.

This study is limited by its retrospective design, subject heterogeneity, variability in timing and dose, incomplete data in some patients, and other confounding factors, e.g., further co-administration of other drugs. Any non-established treatment tends to be administered at the peak of severity of the disease. Therefore, spontaneous improvement, which can occur in SE, cannot be excluded. Given the high number of medications received by patients concomitantly to ketamine, efficacy may be attributed in part to the cumulative or delayed effect of these concurrent or previously administered drugs.

The higher efficacy that was seen with earlier administration may be due to the fact that only the most severe cases persisted long enough for ketamine to be administered. Despite these limitations, this series documents the potential utility and current patterns of use of ketamine for the treatment of RSE and provides useful preliminary data for planning a prospective trial.

Conclusions

Continuous ketamine infusion appeared to be safe and moderately efficient for the treatment of RSE, contributing to the control of SE in one-third of cases, while being responsible for few significant adverse events. The role of ketamine for the treatment of RSE should be further investigated in prospective, randomized trials.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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We confirm that we have read the Journal's position on issues involved in ethical publication and affirm that this report is consistent with those guidelines.

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T.L. serves on the Laboratory Accreditation Board for Long Term (Epilepsy and Intensive Care Unit) Monitoring, on the Council of the American Clinical Neurophysiology Society, on the American Board of Clinical Neurophysiology, as an Associate Editor for Seizure, and performs video electroencephalogram long-term monitoring, electroencephalograms, and other electrophysiological studies at Boston Children's Hospital and bills for these procedures. T.L. receives research support from the National Institutes of Health/NINDS, a Career Development Fellowship Award from Harvard Medical School and Boston Children's Hospital, the Program for Quality and Safety at Boston Children's Hospital, the Payer Provider Quality Initiative, The Epilepsy Foundation of America, the Center for Integration of Medicine and Innovative Technology, the Epilepsy Therapy Project, the American Epilepsy Society, Cure and from investigator initiated research grants from Lundbeck and Eisai. C.D.H. is supported by research grants from the Canadian Institutes of Health Research, PSI Foundation and SickKids Foundation.

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References

Borris DJ, Bertram EH, Kapur J. Ketamine Controls Prolonged Status Epilepticus. Epilepsy Res. 2000; 42:117–122. [PubMed: 11074184]

Brophy GM, Bell R, Claassen J, Alldredge B, Bleck TP, Glauser T, Laroche SM, Riviello JJ Jr, Shutter L, Sperling MR, Treiman DM, Vespa PM. Neurocritical Care Society Status Epilepticus Guideline Writing Committee. Guidelines for the Evaluation and Management of Status Epilepticus. Neurocrit Care. 2012; 17:3–23. [PubMed: 22528274]

Claassen J, Hirsch LJ, Emerson RG, Mayer SA. Treatment of Refractory Status Epilepticus with Pentobarbital, Propofol, or Midazolam: a Systematic Review. Epilepsia. 2002; 43:146–153. [PubMed: 11903460]

Costello CDJ, Kilbride RD, Cole AJ. Cryptogenic New Onset Refractory Status Epilepticus (NORSE) in Adults-Infectious or Not? J Neurol Sci. 2009; 277:26–31. [PubMed: 19013586]

Federman MD, Kelly R, Harrison RE. Refractory Metabolic Acidosis as a Complication of High-Dose Midazolam Infusion for Pediatric Status Epilepticus. Clin Neuropharmacol. 2009; 32:340–341. [PubMed: 19952873]

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Goodkin GHP, Kapur J. The Impact of Diazepam's Discovery on the Treatment and Understanding of Status Epilepticus. Epilepsia. 2009; 50:2011–2018. [PubMed: 19674049]

Green GSM, Coté CJ. Ketamine and Neurotoxicity: Clinical Perspectives and Implications for Emergency Medicine. Ann Emerg Med. 2009; 54:181–190. [PubMed: 18990467]

Hijazi Y, Bodonian C, Bolon M, Salord F, Boulieu R. Pharmacokinetics and Haemodynamics of Ketamine in Intensive Care Patients with Brain or Spinal Cord Injury. Br J Anaesth. 2003; 90:155–160. [PubMed: 12538370]

Hocker SE, Britton JW, Mandrekar JN, Wijdicks EF, Rabinstein AA. Predictors of Outcome in Refractory Status Epilepticus. Arch Neurol. 2012 Oct.(8):1–6.10.1001/archneurol.2013.578

Holtkamp M, Othman J, Buchheim K, Meierkord H. Predictors and Prognosis of Refractory Status Epilepticus Treated in a Neurological Intensive Care Unit. J Neurol Neurosurg Psychiatry. 2005; 76:534–539. [PubMed: 15774441]

Holtkamp, Martin; Othman, Jalal; Buchheim, Katharina; Masuhr, Florian; Schielke, Eva; Meierkord, Hartmut. A 'Malignant' Variant of Status Epilepticus. Arch Neurol. 2005; 62:1428–1431. [PubMed: 16157750]

Hsieh CY, Sung PS, Tsai JJ, Huang CW. Terminating Prolonged Refractory Status Epilepticus Using Ketamine. Clin Neuropharmacol. 2010; 33:165–167. [PubMed: 20098301]

Kofke WA, Bloom MJ, Van Cott A, Brenner RP. Electrographic Tachyphylaxis to Etomidate and Ketamine Used for Refractory Status Epilepticus Controlled with Isoflurane. J Neurosurg Anesthesiol. 1997; 9:269–272. [PubMed: 9239591]

Kramer AH. Early Ketamine to Treat Refractory Status Epilepticus. Neurocrit Care. 2012; 16:299–305. [PubMed: 22237581]

Mayberg TS, Lam AM, Matta BF, Domino KB, Winn HR. Ketamine Does Not Increase Cerebral Blood Flow Velocity or Intracranial Pressure During Isoflurane/Nitrous Oxide Anesthesia in Patients Undergoing Craniotomy. Anesth Analg. 1995; 81:84–89. [PubMed: 7598288]

Mayer SA, Claassen J, Lokin J, Mendelsohn F, Dennis LJ, Fitzsimmons BF. Refractory Status Epilepticus: Frequency, Risk Factors, and Impact on Outcome. Arch Neurol. 2002; 59:205–210. [PubMed: 11843690]

Mazarati AM, Wasterlain CG. N-Methyl-D-Asparate Receptor Antagonists Abolish the Maintenance Phase of Self-Sustaining Status Epilepticus in Rat. Neurosci Lett. 1999; 265:187–190. [PubMed: 10327162]

Novy J, Logroscino G, Rossetti AO. Refractory Status Epilepticus: a Prospective Observational Study. Epilepsia. 2010; 51:251–256. [PubMed: 19817823]

Pruss H, Holtkamp M. Ketamine Successfully Terminates Malignant Status Epilepticus. Epilepsy Res. 2008; 82:219–222. [PubMed: 18804344]

Roervik S, Stovner JJ. Letter: Ketamine-Induced Acidosis, Fever, and Creatine-Kinase Rise. Lancet. 1974; 2:1384–1385. [PubMed: 4143340]

Rosati A, L'Erario M, Ilvento L, Cecchi C, Pisano T, Mirabile L, Guerrini R. Efficacy and Safety of Ketamine in Refractory Status Epilepticus in Children. Neurology. 2012; 79:2355–2358. [PubMed: 23197747]

Rossetti AO, Milligan TA, Vulliémoz S, Michaelides C, Bertschi M, Lee JW. A Randomized Trial for the Treatment of Refractory Status Epilepticus. Neurocrit Care. 2011; 14:4–10. [PubMed: 20878265]

Sheth RD, Gidal BE. Refractory Status Epilepticus: Response to Ketamine. Neurology. 1998; 51:1765–1766. [PubMed: 9855547]

Synowiec AS, Singh DS, Yenugadhati V, Valeriano JP, Schramke CJ, Kelly KM. Ketamine Use in the Treatment of Refractory Status Epilepticus. Epilepsy Res. 2013 Jan.(28)10.1016/j.eplepsyres.2013.01.007

Ubogu EE, Sagar SM, Lerner AJ, Maddux BN, Suarez JI, Werz MA. Ketamine for Refractory Status Epilepticus: a Case of Possible Ketamine-Induced Neurotoxicity. Yebeh. 2003; 4:70–75.

Walker MC, Smith SJ, Shorvon SD. The Intensive Care Treatment of Convulsive Status Epilepticus in the UK. Results of a National Survey and Recommendations. Anaesthesia. 1995; 50:130–135. [PubMed: 7710023]

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Table 1

Demographics and clinical data (N=60 episodes of RSE)

Age; median (range)	24y	(7m–74y)
Children (<18y)	12	(20%)
Female gender	30	(50%)
Etiology		
Unknown	34	(57%)
Acute symptomatic	20	(33%)
*non-anoxic brain injury**	11	*(18%)*
post-anoxic encephalopathy	*7*	*(12%)*
*systemic etiology**	*2*	*(3%)*
Remote symptomatic	6	(10%)
Prior history of epilepsy	9	(15%)
Duration of SE (days); median (range)	26.5d	(1h–10m)
CEEG	59	(98%)
Time from onset of SE to CEEG (median, range)	<24h	(0–17d)
Classification of SE		
Generalized convulsive	14	(23%)
Tonic-clonic	*5*	*(8%)*
Myoclonic	*6*	*(10%)*
Tonic	*3*	*(5%)*
Generalized nonconvulsive	3	(5%)
Focal convulsive	*4*	*(7%)*
Epilepsia partialis continua	*2*	*(3%)*
Hemiconvulsive	*2*	*(3%)*
Focal nonconvulsive	38	(63%)
Status epilepticus of infantile spasms	1	(2%)

Data presented as N (row percentage) unless stated otherwise.

Abbreviations: h: hours; d: days; m: months; y: years. CEEG = continuous EEG monitoring; SE = status epilepticus.

* Causes of non-anoxic brain injury and systemic etiologies included proven infectious (N=4) or autoimmune (N=2; both anti-NMDA) meningo-encephalitis, subarachnoid hemorrhage (N=2), ischemic stroke (N=2), traumatic brain injury (N=1), sepsis-associated encephalopathy (N=1) and posterior reversible encephalopathy syndrome (N=1).

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Table 2

Determinants of ketamine efficacy (N=60 episodes)

	Likely response (N=7)	Possible response (N=12)	*Likely or possible response (N=19)*	No response (N=41)	p-value$ (univ.)	p-value (multiv.)
Latency to ketamine; median (range)	12h (6h–7d)	5d (18h–30d)	*4.5d (6h–30d)*	10d (12h–122d)	0.0053	NS
Number of previously failed drugs; median (range)	4 (3–7)	6 (3–11)	*6 (3–11)*	8 (3–16)	0.0012	< 0.01
Etiology					< 0.001	NS
Unknown (N=34)	1	7	*8*	26		
Anoxic (N=7)	4	0	*4*	3		
Acute non-anoxic (N=13)	2	2	*4*	9		
Remote (N=6)	0	3	*3*	3		
SE classification					NS	-
Generalized convulsive (N= 14)	2	4	*6*	8		
Generalized nonconvulsive (N=3)	0	1	*1*	2		
Focal convulsive (N=4)	0	2	*2*	2		
Focal nonconvulsive (N=38)	5	5	*10*	28		
Infantile spasms (N=1)	0	0	*0*	1		
Maximum infusion rate (mg/kg/h); median (range) *	7 (0.9–10)	1.8 (0.6–7)	*2 (0.6–10)*	3 (0.05–10)	NS	-
Loading dose administered **	6/6 (100%)	5/8 (63%)	*11/14 (79%)*	23/32 (72%)	NS	-
Duration of administration	1 (0–2)	3 (0–10)	*2 (0–10)*	5 (0–27)	< 0.001	NS
Number of concurrent drugs	3 (1–5)	5 (1–11)	*4 (1–11)*	6 (1–10)	< 0.001	NS
Number of concurrent anesthetic drugs ***	1 (0–1)	1 (1–3)	*1 (0–3)*	2 (1–3)	< 0.001	NS

Abbreviations: h = hours; d = days; m = months; univ. = univariate analysis; multiv. = multivariate analysis;

* information available in 54/60 cases;

** information available in 46/60 cases;

*** anesthetic drugs included pentobarbital, thiopental, midazolam and propofol.

$ p value refers to analysis using likely, possible and no response as three separate categories.

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Table 3

Variables associated with mortality

(N=60 cases)	Alive at discharge (N=34; 57%)	Deceased (N=26; 43%)	p-value (univ.)	p-value (multiv.)	OR (multiv.)
Duration of ketamine; days; median (range)	4 (0–24)	4 (0–27)	NS	-	-
Dose of ketamine; mg/kg/h; median (range)	1.7 (0.05–10)	3.6 (0–10)	NS	-	-
Response to ketamine (N=19); N (row %)	16 (84%)	3 (16%)	0.0014	0.001	0.007–0.3
Age; years; median (range)	26 (7mo–85)	51 (19–76)	0.0025	<0.001	1.02–1.1/year
Etiology			0.0127	NS	-
Unknown (N=34); N (row %)	18 (53%)	16 (47%)			
Anoxic (N=7); N (row %)	2 (29%)	5 (71%)			
Acute non anoxic (N=13); N (row %)	9 (69%)	4 (31%)			
Remote (N=6); N (row %)	5 (83%)	1 (17%)			
Status classification			NS	-	-
Generalized convulsive (N=14); N (row %)	8 (56%)	6 (44%)			
Generalized nonconvulsive (N=3); (row %)	1 (33%)	2 (67%)			
Focal convulsive (N=4); N (row %)	2 (50%)	2 (50%)			
Focal nonconvulsive (N=38); N (row %)	25 (66%)	13 (33%)			
Status epilepticus of infantile spasms; N (row %)	1 (100%)	0 (0%)			
Any adverse event (N=18); N (row %)	8 (44)	10 (66%)	NS	-	-
Concurrent anesthetic drugs *; median (range)	2 (0–3)	2 (1–3)	NS	-	-

Abbreviations: univ. = univariate analysis; multiv. = multivariate analysis;;

* anesthetic drugs include pentobarbital, thiopental, midazolam and propofol.

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Table 4

Variables associated with adverse events occurring during ketamine infusion

Adverse events occurring during ketamine infusion (N=60 cases)	Adverse events (N=18; 30%)	No adverse events (N=42; 70%)	p-value (univ.)
Duration of ketamine; days; median (range)	5 (1–17)	3 (0–27)	NS
Maximal infusion rate *; mg/kg/h; ; median (range)	2.4 (0.6–7.5)	2.75 (0–10)	NS
Shock prior to ketamine (N=8); N (row %)	2 (25%)	6 (75%)	NS
Hepatic failure prior to ketamine (N=6); N (row %)	0 (0%)	6 (100%)	NS
Renal failure prior to ketamine (N=10); N (row %)	4 (40%)	6 (60%)	NS
Cardiac failure prior to ketamine (N=7); N (row %)	1 (14%)	6 (86%)	NS
Concurrent antiepileptic drugs; median (range)	5 (4–11)	5 (1–11)	NS
Concurrent anesthetic drugs **; median (range)	2 (1–3)	1 (0–3)	0.005

Abbreviations: h = hours; d = days; m = months; y = years; univ. = univariate analysis; multiv. = multivariate analysis;

* information available in 54/60 cases;

** anesthetic drugs include pentobarbital, thiopental, midazolam and propofol.