Ketamine: Is It Pro-Epileptic or Anti-Epileptic? The Debate Continues. A Narrative Review with a Case Discussion.

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Ketamine is one of the old anaesthetic agents which has regained popularity in analgesia, trauma, emergency medicine, neurology and psychiatry. Recently several cases were reported on ketamine induced seizures in otherwise healthy children despite its popularity in the treatment of refractory status epilepticus. We present an eight-year-old prematurely born healthy boy who developed two episodes of generalized tonic clonic seizures following administration of ketamine for a short ophthalmic procedure. This case and our comprehensive narrative review of literature on pro- and anti-epileptic effects of ketamine show that the debate continues and gaps on mechanism of action, etiology and risk factors for ketamine's epileptic activity remains. Due to the recent increase in its use further evaluation on ketamine's epileptic effects is warranted to ensure safe and effective use of ketamine.

Key words: ketamine, new onset seizures, refractory status epilepticus, neuropharmacology, proepileptic

Introduction

Ketamine is a general anesthetic agent developed in 1962 by the Parke-Davis (USA) pharmaceutical company.[1] Dissociative anaesthesia and sympathetic stimulation are its unique features.[2] It had been a popular anaesthetic in the battle field and in the induction of hypotensive patients.[2,3] Due to several unfavorable properties such as hallucinations on arousal it became less popular among most anaesthetists.[4] The use of this old drug is recently revisited because of its place in pain management, refractory status epilepticus (RSE) and treatment-resistant depression.[1,3,4]

Many studies and case reports are published showing its efficacy as a treatment for drug resistant status epilepticus.[5,6,7] However, traditionally, the use of ketamine was always doubted in the background of epilepsy. We report occurrence of two consecutive seizures in an eight-year-old boy who was given ketamine for a short ophthalmic procedure, with a narrative review of ketamine's pro epileptic and anti-epileptic effects.

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Case presentation

An eight-year-old healthy boy with a weight of 20kg, presented for examination of the eye under anaesthesia following a recent change in vision. He was a preterm baby, born at 28 weeks of gestation and had neonatal intensive care for 14 days. He had retinopathy of prematurity. He did not have epilepsy and his development was age appropriate. We administered 2mg/kg of ketamine intravenously. About 30 seconds later, he developed generalized rigidity followed by a generalized tonic clonic seizure. Seizure lasted for 1 minute and settled with 2mg of midazolam. A minute later, another episode of generalized tonic clonic seizure was noted which lasted for 15 seconds and resolved spontaneously. The procedure was abandoned. His cardiovascular and respiratory parameters, blood sugar, blood gas values, renal and liver function tests, calcium and magnesium levels and EEG (electroencephalogram) were normal. During the six month follow up period he did not have any seizures. He had the eye examination two weeks

later with propofol, fentanyl and sevoflurane without any complications.

Review

Safety concerns of ketamine must be revisited due to its regained popularity in multiple fields. A comprehensive literature review on ketamine's pro and anti epileptic properties were done in Medline, Pubmed, Google scholar and CINAHL databases using "ketamine, ketamine induced seizure, epilepsy, status epilepticus, and peadiatric seizure" as keywords.

The complex neuropharmacological actions of ketamine are mediated through both NMDA and non-NMDA receptors, nicotinic and muscarinic cholinergic, monoaminergic and opioid receptors, and ion channels such as Na and L-type Ca channels.[8] The exact mechanisms for contradictory pro- and anti-epileptic effects are not yet known but postulated to be related to the complexity of the neuropharmacology of ketamine or molecular differences of the brain such as the number, strength, and composition of NMDA receptor containing synapses.[9,10]

A study reported in 1974 on ketamine's effect on both healthy volunteers and patients with epilepsy has revealed that ketamine does not produce EEG changes suggestive of seizures or epileptic activity in both groups.[11] However new evidence is emerging on ketamine's pro epileptic and antiepileptic properties.

Ketamine as an anti-epileptic:

Evidence for the anti-epileptic effects of ketamine goes back to McCarthy et al.'s first discovery of ketamine's antiepileptic activity in animal studies in 1965.[12] These results were soon confirmed with human studies, indicating that ketamine can be used as a possible treatment agent in RSE[13]. Since then, many studies were carried out adding more information to the available literature.

The current theory of using it as an antiepileptic drug arose from the discovery of NMDA's effect in producing grand mal seizures. Increase in NMDA activity can cause seizures; hence NMDA antagonists may be used to control seizures. This is particularly important in status epilepticus, because with prolong seizures there is gradual down regulation of active GABA receptors and upregulation of NMDA receptors.[3,13] Hence the routine antiepileptic drugs acting via GABA receptors such as benzodiazepines, phenobarbitone, propofol and valproate have limited effects in RSE.

There are several studies, case reports and reviews published on the use of ketamine in RSE revealing that ketamine is safe and effective as an antiepileptic agent in RSE.[3,5,14,15] Ketamine's effective and relative safety in controlling of multidrug-resistant RSE in children and adults was shown by Fang Y, et al. by reviewing several studies from 1996 to 2014.[5] Another study, published in 2014, suggested that ketamine might be of potential benefit, and has low tendency to develop adverse reactions in both adults and children.[3] Most studies have examined ketamine's effect on RSE in adults.[16] Rosati et al observed that six out of nine children with RSE who received ketamine had responded.[17] There are no randomized controlled studies on ketamine in the treatment of RSE due to ethical issues in establishing a control arm as RSE can cause significant morbidity and mortality. Further the first planned RCT on this was terminated due to insufficient recruitment.[5,18]

There's no data on ketamine's use as a monotherapy or first line therapy for seizure management but it has shown better results when used in RSE refractory to two or more antiepileptics.[9] It appears to work either additive or synergistically with other antiepileptics.[9] The suggested dose is 5 mg/kg intravenous bolus followed by a continuous infusion gradually titrated up to 1.5 mg/kg/hour.[9] Oversedation, respiratory depression, need for intubation, and haemodynamic instability that would occur with high doses of other antiepileptics will be minimized by ketamine. However, despite availability of some literature, ketamine's use has not yet been included in the guidelines for the treatment of RSE.

Ketamine as a pro-epileptic:

Despite its development as an anti-epileptic agent, there is still a concern on its epileptogenic action. Most of the evidence supporting pro-

convulsive action of ketamine origin in early 21st century probably due to its recent frequent use. Our case too describes occurrence of two episodes of seizures after administration of ketamine in a healthy child born prematurely. There are several case reports on seizure activity following the use of ketamine.[19,20,21,22]

Noaimi reports a healthy six-year-old boy who received IV ketamine for a facial laceration repair and developed a tonic clonic seizure for about 30 seconds.[19] Kandrani et al report an otherwise healthy 10-year-old boy patient who received IM ketamine for a tonsillectomy and developed a seizure.[20] Meaden et al report a 15-year-old girl who received IM ketamine for procedural sedation and had a self-limiting seizure episode for one minute. She was a known patient with autism with a stable mental status and CT brain showed mild colpocephaly of the ventricles of uncertain significance and a normal one-hour EEG.[21] Kim et al report a seven-year-old healthy boy who had a seizure following ketamine for sedation to repair a laceration.[22] Interestingly all patients are in the paediatric age group. Three patients received IM ketamine (2-4mg/kg) and one patient received 1mg/kg IV ketamine, which are in the accepted dose range. All patients had tonic-clonic seizures lasting 30 sec to one minute, settling spontaneously or with a dose of benzodiazepine and there were no repeated episodes of seizures. They had normal follow up EEGs. None of them had previous seizures or known seizure precipitants.

Even though our patient was born preterm, he had no epilepsy or cerebral pathologies. There are case reports and studies on ketamine's use in premature babies for surgeries or interventions for retinopathy of prematurity but none of these report about seizures and it was found to be safe.[23,24] Hence, whether prematurity makes him vulnerable to cause seizures by ketamine is questionable.

Literature related to adult ketamine induced seizures are different. Green et al report that three out of 17 mentally disabled adults who had ketamine for procedural sedation developed transient tonic clonic seizures. However, all three had a history of epilepsy and two of them had daily seizures despite on antiepileptics, hence whether the seizures were related to ketamine is questionable.[25] A review published in 2007 examining ketamine for procedural sedation has not shown any new onset seizures related to ketamine in healthy adults.[26]

The etiology of ketamine induced seizures is yet unknown. Probably the paediatric age group is more vulnerable than adults as all above five cases are children. The dose, route of administration, gender, or presence of prematurity or autism are yet be evaluated as possible risk factors, hence warrants further studies.

Conclusion

It seems the dilemma of ketamine's pro-epileptic and anti-epileptic effects continues. Considering the presented case report and other similar cases published, one must consider its potential for causing seizures in normal individuals especially in children as intra operative seizures can be detrimental. For safer use of ketamine, the risk factors and aetiology for seizures must be further evaluated as its use has again increased.

References

1. Kurdi, Madhuri S et al. Ketamine: Current applications in anesthesia, pain, and critical care. *Anesthesia, essays and researches* 2014. **8**(3): 283-90. doi:10.4103/0259-1162.143110
2. Pai A, Heining M. Ketamine: *Contin Educ Anaesth Crit Care Pain* 2007;**7**(2):59-63. doi: 10.1093/bjaceaccp/mkm008
3. Mion G, Villevieille T. Ketamine Pharmacology: An Update Pharmacodynamics and Molecular Aspects, Recent Findings. *CNS Neurosci Ther* 2013, **19**:370-380. https://doi.org/10.1111/cns.12099
4. Kim J, Farchione T, Potter A, et al. Esketamine for Treatment-Resistant Depression - First FDA-Approved Antidepressant in a New Class. *N Engl J Med*. 2019;**381**(1):1-4. doi:10.1056/NEJMp1903305
5. Fang Y, Wang X. Ketamine for the treatment of refractory status epilepticus. *Seizure*. 2015 Aug;**30**:14-20. doi:10.1016/j.seizure.2015.05.010. Epub 2015 May 19. PMID: 26216679.

6. Synowiec AS, Singh DS, Yenugadhati V, et al. Ketamine use in the treatment of refractory status epilepticus. *Epilepsy Res*. 2013 Jul;**105**(1-2):183-8. doi: 10.1016/j.eplepsyres.2013.01.007. Epub 2013 Jan 29. PMID: 23369676.
7. Michael A. P, Prasuna K, William O. T, et al. Freeman, Transition from intravenous to enteral ketamine for treatment of nonconvulsive status epilepticus. *Journal of Intensive Care* 2017; **5**:54 DOI 10.1186/s40560-017-0248-6
8. Kohrs R, Durieux ME. Ketamine: Teaching an old drug new tricks. *Anesth Analg* 1998;**87**:1186–1193
9. Pribish A, Wood N, Kalava A. A Review of Nonanesthetic Uses of Ketamine. *Anesthesiol Res Pract*. 2020;5798285. Published 2020 Apr 1. doi:10.1155/2020/5798285
10. Choudhury D, Autry AE, Tolias KF, et al. Ketamine: Neuroprotective or Neurotoxic*?*. *Front Neurosci*. 2021;15:672526. Published 2021 Sep 10. doi:10.3389/fnins.2021.672526
11. Corssen G, Little S, Tavakoli M. Ketamine and epilepsy. *Anesthesia & Analgesia*. 1974;**53**(2):319–35
12. D. McCarthy, G. Chen, D.H. Kaump, C. Ensor. General anesthetic and other pharmacological properties of 2-(O-chlorophenyl)-2-methylamino-cyclohexanone HCl (CI-58L) *J New Drugs* 1965; **5** :21-33
13. G. Corssen, M. Miyasaka, E.F. Domino. Changing concepts in pain control during surgery: dissociative anesthesia with CI-581. A progress report. *Anesth Analg* 1968; **47**:746-759
14. A Alkhachroum, C. A. Der-Nigoghossian, E Mathews, et al. Ketamine to treat super-refractory status epilepticus *Neurology* 2020:,**95**(16):2286-2294; DOI: 10.1212/WNL.0000000000010611
15. Shrestha G. S., Joshi P., Chhetri S., et al. Intravenous ketamine for treatment of super-refractory convulsive status epilepticus with septic shock: A report of two cases. *Indian journal of critical care medicine* 2015;**19**(5):283–285. https://doi.org/10.4103/0972-5229.156484
16. C.Y. Hsieh, P.-S. Sung, J.-J. Tsai, C.-W. Huang, Terminating prolonged refractory status epilepticus using ketamine, *Clinical Neuropharmacology* 2010;**33**(3):165–167.
17. Rosati A, L'Erario M, Ilvento L, et al. Efficacy and safety of ketamine in refractory status epilepticus in children. *Neurology* 2012;**79**(24):2355-2358. doi:10.1212/WNL.0b013e318278b68
18. Fernandez, J. Claassen. Refractory status epilepticus. *Curr Opin Crit Care* 2012;**18**:127-131
19. M Al Noaimi, S Hussain, G Al Qassim: Ketamine Induced Generalized Convulsive Seizure in a Healthy 6-Year-Old Male Undergoing Procedural Sedation; *Bahrain Med Bull* 2020;**42**(1):79 – 80
20. Khandrani, Jitesh et al. Ketamine Induced Seizures. *The Internet Journal of Anesthesiology* 2008;**19**(1)
21. Meaden CW, Barnes S. Ketamine Implicated in New Onset Seizure. *Clin Pract Cases Emerg Med*. 2019;**3**(4):401-404. Published 2019 Oct 21. doi:10.5811/cpcem.2019.9.44271
22. Kim JH, Lee CK, Yu SH, et al. Ketamine-induced generalized convulsive seizure during procedural sedation. *Arch Craniofac Surg*. 2021;**22**(2):119-121. doi:10.7181/acfs.2021.00094
23. F. Lyon, T. Dabbs, M. O'Meara. Ketamine sedation during the treatment of retinopathy of prematurity. *Eye* 2008; **22**: 684–686
24. Louon, J. Lithander, et al. Sedation with nasal ketamine and midazolam for cryotherapy in retinopathy of prematurity. *Br J Ophthalmol*. 1993 Aug; **77**(8): 529–530.
25. Green SM, Rothrock SG, Hestdalen R, et al. Ketamine sedation in mentally disabled adults. *Acad Emerg Med*. 1999;**6**(1):86-87. doi:10.1111/j.1553-2712.1999.tb00102.x
26. R J. Strayer, L S. Nelson. Adverse events associated with ketamine for procedural sedation in adults, *The American Journal of Emergency Medicine* 2008;**26**(9):985-1028, ISSN 0735-6757, https://doi.org/10.1016/j.ajem.2007.12.005