

## Resurfacing of ketamine: The subanesthetic paradigm

“Infinite diversity in infinite combinations... symbolizing the elements that create truth and beauty.” -Commander Spock.

Ketamine is probably the drug that will qualify for being used for maximally divergent anesthetic and nonanesthetic clinical effects in the widest variety of doses and with an innumerable combination with other drugs. Despite its broad clinical benefits, it was never really recognized as a favored drug in the anesthesiologist's armamentarium and bided its time being useful to fringe practitioners (read anesthesiologists providing services in nontertiary care setups!). The resurgence of ketamine as a mainstream drug, however, owes its extensive usefulness in low- or sub-anesthetic doses.

Ketamine is a noncompetitive N-methyl-D-aspartate receptor (NMDAR) antagonist and acts by binding to the open ion channel of these receptors and preventing ion and current flow through them, the NMDARs are intricately and intimately associated with not only the occurrence of acute pain but also the development of opioid tolerance, opioid-induced hyperalgesia, and chronic pain by the mechanism of suppression of central sensitization.<sup>[1]</sup> The multiple sites of NMDARs in central, spinal, and peripheral nervous tissue beget equally multiple clinical effects. The main reason for the reluctance by the anesthesiologists to use the drug seems to be its potent psychomimetic effects including hallucinations and dysphoria, central sympathomimetic effects, variable increase in intraocular and intracranial pressure, inconsistent effect on seizure threshold, and a consistent increase in salivary and respiratory secretions. The powerful psychomimetic side effects are also the reason for its abuse potential. Most of these side effects, however, are commonly and pronouncedly seen with higher doses of ketamine, usually >0.5 mg/kg. The so-called anesthetic doses (dose at which dissociative anesthesia is induced in patients) are typically  $\geq 1$  mg/kg. The recent interest in ketamine primarily lies in its divergent uses but without its unpleasant side effects and utilizes low- or sub-anesthetic doses of the drug.

In recent times, scores of different nonanesthetic uses of low-dose ketamine have been explored. Some of these uses are now validated indications for ketamine. Subanesthetic doses of ketamine have been used successfully in the treatment of chronic regional pain syndrome and other chronic pain

disorders.<sup>[2]</sup> The use of low-dose ketamine as adjuvant to other drugs is also widely practiced in patients with refractory cancer pain.<sup>[3]</sup> One of the most exciting developments is its use for the treatment for major and refractory depression.<sup>[4]</sup> There is also a renewed interest in its use in the treatment of acute pain in the emergency department.<sup>[5]</sup> Off-label and incidental use of ketamine in subanesthetic doses has been reported for many other indications including refractory status epilepticus,<sup>[6]</sup> acutely exacerbated and/or refractory asthma,<sup>[7]</sup> and vaso-occlusive crisis in sickle cell disease.<sup>[8]</sup> Anesthesiologists, of course, have been using it safely and consistently for procedural sedation, gastrointestinal endoscopy, bronchoscopy, and even postoperative analgesia. The possibility of its usefulness in low doses has opened up new avenues for its use in perioperative period as well.

Subanesthetic dose of ketamine has been found to be associated with many advantages when used during surgical procedures either under regional or general anesthesia.<sup>[9]</sup> The use of low-dose infusion of perioperative ketamine was seen to be associated with decreased opioid consumption in the intra- and post-operative period in patients undergoing orthopedic and spine surgery under general anesthesia in a few recent studies.<sup>[10-12]</sup> Interestingly, low-dose ketamine infusion was also found to improve the cognitive dysfunction in elderly patients undergoing ophthalmic procedures under retrobulbar block with intravenous sedation utilizing midazolam and fentanyl.<sup>[13]</sup> The role of ketamine in decreasing the perioperative immune response is also a subject of recent research which has shown positive results although more studies are required to evaluate and evidence the issue with certainty.<sup>[14,15]</sup>

In the previous edition of the journal, Gorlin *et al.*, from Mayo Clinic, Arizona, Phoenix, have reviewed the usage of ketamine in subanesthetic doses for perioperative analgesia.<sup>[16]</sup> Despite many studies and reviews utilizing the drug in so-called “subanesthetic,” “subdissociative,” and “low-dose” ketamine, the actual dose and route of administration of ketamine for the said purpose remain undefined. Gorlin *et al.* have provided a practical guide to this in the review with suggested dosages for boluses and infusions in the perioperative period for various kinds of surgical procedures. In continuance with this previous review, Vadivelu *et al.*, elaborate more on the overall role of ketamine in anesthesia and non-anesthesia practice in the present issue.<sup>[9]</sup>

It, thus, may be expected that with more recommendations and reasons to use low-dose ketamine and with our increasing use of ketamine, more such guidelines would be available inducing the mainstream anesthesiologists to use the drug

utilizing its infinite diversity with infinite combination to its maximum advantage.

“...I like to believe that there are always possibilities.” -Commander Spock.

### Rashmi Ramachandran, Vimi Rewari

Department of Anaesthesiology, All India Institute of Medical Sciences, New Delhi, India

**Address for correspondence:** Dr. Rashmi Ramachandran, Department of Anaesthesiology, Room No: 5013, All India Institute of Medical Sciences, Ansari Nagar, New Delhi - 110 029, India. E-mail: rashmiramachandran1@gmail.com

## References

- Johnson JW, Glasgow NG, Povysheva NV. Recent insights into the mode of action of memantine and ketamine. *Curr Opin Pharmacol* 2015;20:54-63.
- Sheehy KA, Muller EA, Lippold C, Nouraei M, Finkel JC, Quezado ZM, *et al.* Subanesthetic ketamine infusions for the treatment of children and adolescents with chronic pain: A longitudinal study. *BMC Pediatr* 2015;15:198.
- Hardy J, Quinn S, Fazekas B, Plummer J, Eckermann S, Agar M, *et al.* Randomized, double-blind, placebo-controlled study to assess the efficacy and toxicity of subcutaneous ketamine in the management of cancer pain. *J Clin Oncol* 2012;30:3611-7.
- Romeo B, Choucha W, Fossati P, Rotge JY. Meta-analysis of short- and mid-term efficacy of ketamine in unipolar and bipolar depression. *Psychiatry Res* 2015;230:682-8.
- Ahern TL, Herring AA, Anderson ES, Madia VA, Fahimi J, Frazee BW. The first 500: Initial experience with widespread use of low-dose ketamine for acute pain management in the ED. *Am J Emerg Med* 2015;33:197-201.
- Fang Y, Wang X. Ketamine for the treatment of refractory status epilepticus. *Seizure* 2015;30:14-20.
- Kiureghian E, Kowalski JM. Intravenous ketamine to facilitate noninvasive ventilation in a patient with a severe asthma exacerbation. *Am J Emerg Med* 2015;33:1720.e1-2.
- Neri CM, Pestieau SR, Darbari DS. Low-dose ketamine as a potential adjuvant therapy for painful vaso-occlusive crises in sickle cell disease. *Paediatr Anaesth* 2013;23:684-9.
- Vadivelu N, Schermer E, Kodumudi V, Belani K, Urman RD, Kaye AD. Role of ketamine for analgesia in adults and children. *J Anaesthesiol Clin Pharmacol* 2015;31:1-9.
- Pacreu S, Fernández Candil J, Moltó L, Carazo J, Fernández Galinski S. The perioperative combination of methadone and ketamine reduces post-operative opioid usage compared with methadone alone. *Acta Anaesthesiol Scand* 2012;56:1250-6.
- Nitta R, Goyagi T, Nishikawa T. Combination of oral clonidine and intravenous low-dose ketamine reduces the consumption of postoperative patient-controlled analgesia morphine after spine surgery. *Acta Anaesthesiol Taiwan* 2013;51:14-7.
- Martinez V, Cymerman A, Ben Ammar S, Fiaud JF, Rapon C, Poindessous F, *et al.* The analgesic efficiency of combined pregabalin and ketamine for total hip arthroplasty: A randomised, double-blind, controlled study. *Anaesthesia* 2014;69:46-52.
- Rascón-Martínez DM, Fresán-Orellana A, Ocharán-Hernández ME, Genis-Zarate JH, Castellanos-Olivares A. The effects of ketamine on cognitive function in elderly patients undergoing ophthalmic surgery: A pilot study. *Anesth Analg* 2016;122:969-75.
- Dale O, Somogyi AA, Li Y, Sullivan T, Shavit Y. Does intraoperative ketamine attenuate inflammatory reactivity following surgery? A systematic review and meta-analysis. *Anesth Analg* 2012;115:934-43.
- Beilin B, Rusabrov Y, Shapira Y, Roytblat L, Greemberg L, Yardeni IZ, *et al.* Low-dose ketamine affects immune responses in humans during the early postoperative period. *Br J Anaesth* 2007;99:522-7.
- Gorlin AW, Rosenfeld DM, Ramakrishna H. Intravenous sub-anesthetic ketamine for perioperative analgesia. *J Anaesthesiol Clin Pharmacol* 2016;32:160-7.

This is an open access article distributed under the terms of the Creative Commons Attribution-NonCommercial-ShareAlike 3.0 License, which allows others to remix, tweak, and build upon the work non-commercially, as long as the author is credited and the new creations are licensed under the identical terms.

Access this article online	
Quick Response Code:	Website: www.joacp.org
	DOI: 10.4103/0970-9185.188823

**How to cite this article:** Ramachandran R, Rewari V. Resurfacing of ketamine: The subanesthetic paradigm. *J Anaesthesiol Clin Pharmacol* 2016;32:286-7.