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Title: Comeback of Ketamine: Resurfacing facts and dispelling myths

Author names and affiliations:

1. ABHIJIT KUMAR, MD
Department of Anesthesiology VMMC and Safdarjung Hospital New Delhi, India
abhijit.kumar999@gmail.com
ORCID: https://orcid.org/0000-0001-5724-8603

2. AMIT KOHLI, MD
Department of Anesthesiology Maulana Azad Medical College New Delhi, India
dramitkohli@yahoo.com
ORCID: https://orcid.org/0000-0002-1885-3461

Corresponding Author:

Amit Kohli, MD
Department of Anesthesiology Maulana Azad Medical College New Delhi, India
E mail: dramitkohli@yahoo.com
Postal address: 2/52 Subhash Nagar, New Delhi 110027, India

Authors credits:

ABHIJIT KUMAR: Conceptualization, Methodology, software, formal analysis, Writing-original draft, Visualization

AMIT KOHLI: Conceptualization, Methodology, Resources, Writing-original draft, Writing- review and editing

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Comeback of Ketamine: Resurfacing facts and dispelling myths

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Abstract

Initially known as CI-581, ketamine was first synthesized in 1962 as a replacement for phencyclidine (PCP). It is being used since then as a profound anesthetic and analgesic, in addition has bronchodilating, sedative and amnestic properties with the preservation of airway reflexes and sympathetic nervous system tone. Ketamine is always a stimulating topic of discussion since its discovery as the controversies regarding its usage in certain set of patients mostly overpowers its boon. In past 50 years, despite of potential benefits it has not gained acceptable popularity because of concerns of “emergence phenomenon”, its use as substance of abuse and systemic side effects. Since 2012, ketamine has been subject to three World Health Organization (WHO) reviews addressing its international control.

Researchers are widely studying this wonder drug since a decade worldwide. Many myths of ketamine regarding emergence phenomenon, its use in traumatic brain injury, open eye injury is getting busted in recent times. It’s again getting popular in pre-hospital settings, critical care, emergency medicine, low dose acute pain services & adjuvant in regional anesthesia techniques. This review will highlight the current consensus on the various applications of ketamine in the light of available evidence in the literature.

Keywords: Ketamine, Intracranial pressure, intraocular pressure, acute pain services, chronic cancer pain, emergence reaction, alcohol withdrawal, status epilepticus.
Introduction

Ketamine is a versatile drug with its unique profile permitting its usage in battery of situations throughout the globe. The variable dosing regimens makes it a wonderful agent for induction of anesthesia in high dosages with preservation of protective reflexes whereas a potent analgesic in low dose infusions. With the advent of newer and considerably safer drugs along with its problems of abuse, ketamine was losing its sheen. It was a pray of traditional stigma even among practitioners worldwide. Very recently researchers across the globe has gained interest in ketamine and literature is available as “myth busters” of this agent in the era of evidence based practices.

This article will highlight the controversies related to psychosomatic issues related to ketamine. The authors will also discuss the evidence and consensus about its use in patients with raised intracranial and intraocular pressures. Role of ketamine in acute as well as chronic pain services and critical settings will also be discussed.

Birth of Ketamine and its timeline

Calvin Stevens in 1962 at Parke Davis laboratory synthesize a compound known as CL 581 from phencyclidine which he later named it as Ketamine.

1964: Its first use as anesthetic on prisoners in Michigan state prison by Dr. Corssen

1968: After Food and Drug Administration approval, ketamine anesthesia was first used on American soldiers during the Vietnam War.


Early 1980’s: Emergence phenomenon led to increasing illicit use and withdrawn from mainstream anesthetic use in human

2000: Antidepressant effects of ketamine in resistant cases by Dr Berman at Yale
2002: Continuous infusions gained popularity in intractable complex regional pain syndrome by Dr Harbert and Correl at Yale.

2013: Shifted from Schedule H to Schedule X drug to prevent its use as per Drugs and Cosmetics act

2014: Effect of ketamine on suicidal ideation by Dr Price at Yale and as treatment of posttraumatic stress disorder

2015: Large scale persistent network reconfiguration demonstration by Dr Yang

**Pharmacology**

It’s a phencyclidine derivative and a noncompetitive N-Methyl-D-Aspartate (NMDA) receptor antagonist which blocks the phencyclidine sites on NMDA receptors mostly present in cerebral cortex, thalamus, limbus and the spinal cord which in turn leads to neuronal depolarization *(Figure 1)*. Its analgesic action is mainly due to its effects on opioid receptors. Other than regular intravenous route, it can also be given intramuscularly, intranasally and interosseously.

It is highly lipid soluble and has low protein binding capacity. It gets metabolized primarily in liver via hydroxylation and N-demethylation into Nor-ketamine which is 30% as potent as ketamine with weak analgesic property.

**Systemic effects: What anesthesiologist should know?**

**Cardiovascular:** In patients with normal autonomic activity, it has a central sympathomimetic action leading to tachycardia, hypertension and increased cardiac output. It’s because of this on one hand this is agent of choice for inductions in acute hypovolemic shock whereas it’s to be avoided in patients with coronary artery diseases. It is worth noting that in patients with depleted catecholamines as in chronic
In shock and critically ill patients it has negative inotropic effect which further accentuates shock like state. If autonomic activity is normal sympathomimetic effects over rides negative inotropic action [1].

**Respiratory:** It’s an established fact that ketamine preserves airway tone, laryngo-pharyngeal reflex and causes bronchodilation. However in infants airway reflexes are very unpredictable [2]. Here it is worth mentioning that use of intravenous ketamine in large boluses can lead to transient apnea as it may have slight respiratory depressant effect and decreases the stimulant action of hypercarbia [3].

**Miscellaneous:** Ketamine also affects metabolic and endocrine system. It increases blood glucose, plasma cortisol and prolactin levels [1]. It also leads to excessive salivation, thus some clinicians advocate routine use of an antisialagouge with it.

Ketamine, since the days of its discovery has remained into controversy simply because of dogmas associated with it. Authors of this article really wish to bust the myths associated with it and highlight facts in evidence based manner.

**Consensus on ketamine use: What evidence speaks?**

**Ketamine in traumatic brain injury:**

“Elevated intracranial pressure with ketamine” is one of the biggest controversy that persists regarding the use of it in patients with a head injury. Some researchers emphasize that ketamine can cause a rise in intracranial pressure (ICP) through sympathetic stimulation, potentially exacerbating the condition. However, when ketamine is used with a γ-aminobutyric acid (GABA) agonist, this rise in ICP may not occur [4]. Furthermore, by increasing cerebral perfusion, ketamine may benefit patients with a neurologic injury. So, now the question is from where this thought that ketamine leads to increased ICP originated? On thorough literature search authors found that there were a series of six studies published in 1970s that reported an association with increased ICP. To further add to it, all of this research was
comprised of case reports and small case control studies. These publications were confounded by patients with abnormal cerebrospinal fluid pathways, which included patients with aqueductal stenosis and obstructive hydrocephalus [5]. None of these studies have directly evaluated the effect of ketamine in patients with traumatic brain injuries (TBI). Unfortunately, the myth that ketamine was contraindicated with TBIs has persisted until recently when some big time studies came up with conflicting results. Many recent studies had directly studied the effects of ketamine on ICP in TBI patients and strongly came up with the fact that ketamine is now rather one of the best agents to facilitate airway management in the head injury cases [6]. A large systematic review based on Cochrane methodology having Oxford level 2b, GRADE C evidence also support that ketamine does not increase ICP in sedated and ventilated cases of severe TBI, and in fact may lower it in some of the study patients [7]. Priorities in TBI patients include: maintaining mean arterial pressure (MAP), preventing hypoxia and hyperventilation, and mitigating increases in ICP. Ketamine assists in accomplishing these priorities. Ketamine retains the patient's respiratory drive, doesn't decrease blood pressure, yields no increase in ICP, and allows for an additional advantage over other sedation medications as well as behavioral control without apnea [8]. Recent publications have shown evidence for ketamine's role in neuroprotection [9]. In addition to it, having an intravenous (IV) access to administer ketamine is not mandatory as it can be given intramuscular (IM) or through intranasal route so can easily be used in emergency settings [10]. Lastly, ketamine has a high therapeutic index that allows some flexibility in dosing it is necessary when obtaining an accurate body weight isn't possible [11].

**Consensus:** Ketamine can safely be used in patients with traumatic brain injury as no large trials have proved it to increase intracranial pressure in such patients rather it provides hemodynamic stability in such patients.
Ketamine in patients with raised intraocular pressure

The initial work on ketamine and its effects on intraocular pressure (IOP) was done by Corssen and Hoy in 1967 and described an increase of intraocular pressure but study had several limitations [12]. The study looked at patients of different ages undergoing general anesthesia for surgical operations of various kinds. Their data included only fifteen pediatric cases, several of whom had incomplete data. The pre-medications used in the study were not standardized and included agents not generally used in the pediatric age group for this purpose (e.g., barbiturates). The investigators studied the patients for three minutes after drug administration, a time point which alone is not appropriate for the pharmacokinetics of this drug. In almost half of the subjects the measurements either did not change or decreased in one or both eyes. A lesser proportion of IOP elevation was noted in pediatric cases, and these subjects yielded a pooled mean increase of less than 3 mm-Hg from control readings. A landmark study by Drayana PC et al proved that at dosages ≤ 4 mg/kg, there are not clinically meaningful associations of ketamine with IOP [13]. Recently a systematic review comprising of nine studies including 293 patients was published which also suggest that the administration of ketamine in pediatric patients to perform ocular tonometry has little or no effect on intraocular pressure. Two out of the nine studies mentions slight rise in IOP if ketamine doses were more than 4mg/kg [14]. Although further study is warranted to determine if ketamine can be used safely for procedural sedation when elevated IOP or globe injury is a concern.

Consensus: Most of the available literature suggests that ketamine influences IOP in a dose dependent manner. Generally, doses less than 4mg/kg doesn’t lead to increase in IOP, rather at times decreases it but most of the analysis have low level of evidence and further large trials are needed to validate it.
Ketamine in acute pain services

The analgesic characteristics of ketamine are primarily established via the NMDA receptors located at the central nervous system [15] and to some extent through opioid receptors [16]. American Society of Regional Anesthesia (ASRA) and the American Society of Anesthesiologists (ASA) has published an entire consensus on the role of ketamine in acute pain management. They have supported the use of ketamine for acute pain in a variety of contexts, including as a stand-alone treatment, as an adjunct to opioids and especially in opioid tolerant patients. They have recommended that ketamine bolus doses should not exceed 0.35 mg/kg and infusions for acute pain should not exceed 1 mg/kg per hour in settings where there is no intensive monitoring [17]. Ketamine's adverse effects will prevent some patients from tolerating higher doses in acute pain settings and unlike for chronic pain therapy, lower doses (i.e.0.1–0.5mg/kg per hour) may be needed to achieve an adequate balance of analgesia and adverse effects (grade C recommendation, moderate level of certainty). Consensus guidelines also state that clinicians should exclude or limit ketamine use in patients with the commonly considered contraindications. These include severe hepatic dysfunction (cirrhosis) [18] and high-risk coronary artery disease [19]. A recent meta-analysis also reported that patients receiving continuous sub-anesthetic ketamine experienced considerably less pain than those treated by traditional opioid regimens [20].

Another Cochrane systematic review studying 37 randomized controlled trials (RCT’s) also concludes that sub-anesthetic doses of ketamine is effective in reducing morphine requirements in the first 24 hours after surgery and it also reduces postoperative nausea and vomiting which is the main problem with opioids, the most commonly used formulations for postoperative analgesia [21]. Not only for intravenous use its also been studied for perioperative analgesia by various other routes. Feltracco and colleague [22] showed that epidural infusion of sub-anesthetic doses of S(+)-ketamine during thoracic
surgery provides better post-operative analgesia than epidural ropivacaine. Preemptive intranasal ketamine 1.5 mg/kg enhances postoperative analgesia after endoscopic nasal surgery [23]. Ketamine spray (0.5 mg/kg) in tonsillar fossa is effective for post-tonsillectomy pain control in children [24]. Whereas a recent RCT evaluated Low-dose S+ ketamine in target-controlled intravenous anesthesia with remifentanil and propofol for open gynecological surgery concluded that there was no effect on the 24H cumulative morphine consumption with S Ketamine however there was a delayed emergence from general anesthesia reported with S Ketamine [25].

**Consensus:** The applications of ketamine in sub anesthetic doses in the perioperative setting have been associated with reduced pain scores, opioid requirements, and postoperative nausea and vomiting, without any considerable side effects. Moreover, good results have been established on using ketamine for surgery patients with high levels of postoperative pain. Level of evidence is still poor to recommend it as sole agent for perioperative infusions for analgesia, though good level of evidence is present for its use as adjuvant.

**Ketamine for chronic pain**

(a) **Non cancer pain:** The action of ketamine on opiate tolerance and hyperalgesia combined with its direct analgesic activity has prompted its increasing use in chronic pain states [8]. IV ketamine has also been evaluated for phantom limb pain and a study reported that infusion as 300 μg/kg in 60 ml solution over 3 hours had led to complete remission of the same [26]. Low dose intranasal S(+) ketamine is beneficial for the *ad hoc* treatment of breakthrough pain in patients with neuropathic pain [27]. Oral ketamine has a poor safety profile and its efficacy in chronic pain management discourages its use but it may have a limited place as an add-on therapy in complex chronic pain patients if other therapeutic options have failed [28]. However,
the long-term effectiveness of ketamine to treat chronic pain remains controversial, as studies often demonstrate contradicting results. A recent meta-analysis comprising of 6 clinical trials where ketamine was compared to a placebo during chronic non-cancer pain found moderate evidence suggesting the efficacy of ketamine during chronic pain. However they found ketamine increased the incidence of psychedelic manifestations in comparison to placebo. Further studies are warranted in this regard so as to determine optimal administration regimes of this agent during this condition [29]. Connolly et al 2015 [30] in their meta-analysis of 6 studies, Maher et al 2017 [31] reviewed 11 RCT’s and Michelet et al 2018 reviewed 6 RCT’s [32] suggest that there is no high quality evidence available evaluating the efficacy of ketamine for complex regional pain syndrome and all manuscripts examined in this review were of moderate to low quality.

(b) Cancer pain: Ketamine is now considered to be an essential adjuvant analgesic for refractory cancer pain, and it is on the WHO’s essential drugs list for patients who no longer respond to high doses of opioids or have predictable breakthrough pains [33]. Nowadays, ketamine is regarded as an essential adjuvant drug in palliative care in many countries. It could be administered in various regimens through oral, intravenous, intrathecal, subcutaneous, and topical routes of administration [34]. A recently published cochrane systematic review studying ketamine as adjuvant to refractory cancer pain concluded that current evidence is insufficient to assess the benefits and harms of ketamine as an adjuvant to opioids. It was further stated that dose escalation to as high as 500 mg did not lead to any added clinical advantage and rather appear to have serious adverse events [35]. However, a 2012 Cochrane review of the use of ketamine in cancer pain found 2 RCTs suggesting that ketamine as an adjunct to morphine
improves the effectiveness of morphine in cancer pain. This review had 32 case reports, out of them 28 reported an excellent pain relief with ketamine. Adverse effects commonly reported were sedation and hallucinations though they were not severe [35]. One study of 185 participants, in a dose-escalation, double-blind, randomized, placebo-controlled phase III trial, where ketamine or the placebo were delivered subcutaneously over 3 to 5 days concluded that ketamine does not have a net clinical benefit when used as an adjunct to opioids and standard co-analgesics in cancer pain [36]. A literature search revealed four randomized controlled trials that examined the benefit of oral, subcutaneous or intravenous ketamine in opioid refractory cancer pain and none showed clinically relevant benefit in relieving pain or reducing opioid consumption [37].

**Consensus:** Moderate level of evidence is available suggesting use of ketamine in chronic non cancer pain whereas most of the RCT’s presents low level of evidence for its use in cancer pains. However large number of open label studies and retrospective case series advocates its use.

**Ketamine as an antidepressant and role in cognition and schizophrenia?**

Ketamine has proved to be an extremely effective treatment for major depression, bipolar disorder and suicidal behavior. Resistance to the regular antidepressants is the growing concern in patients with Manic Depressive Disorder. The slow onset and moderate degrees of receptor occupancy could largely be used to avoid the anesthesia effect, dissociation and psychotomimetic reactions [38]. Ketamine works incredibly fast, lifting depression in less than two hours, which is unlike conventional antidepressants that generally take weeks to work [39,40]. A systematic review also showed ketamine to be a rapid and effective treatment option for depression, as well as reducing suicidal ideation, with minimal short-term side effects [41]. In 2018 Chen MH etal in their study have found that 0.5 mg/kg
dose of ketamine infusion was beneficial for the cognitive function of patients with treatment resistant depression [42].

Ketamine is a racemic mixture having equal parts of (R)-ketamine and (S)-ketamine. Out of the two, (S)-ketamine was developed as an antidepressant agent owing to its higher affinity for NMDA receptors. On 5 March 2019, (S)-ketamine nasal spray was approved by the US Food and Drug Administration for the same purpose [43].

Although efficacy of ketamine has also been shown in depressed patients with a history of psychotic symptoms, its administration in psychotic disorders has largely been neglected due to its potential to exacerbate dissociative or psychotic symptoms [44].

A study by Duman and Li showed a single injection of ketamine increased prefrontal synaptogenesis and reversed stress-induced atrophy [45]. This is consistent with findings that mice carrying a mutant form of glycogen synthase kinase 3 – an enzyme involved in synaptic plasticity- are unresponsive to ketamine [46].

Research on ketamine is still in its infancy and many facets have remained obscure. For instance, there is no consensus regarding its effects on controlled long-term use. Most studies are conducted with drug abusers in a correlational manner and thus generalization to “physically healthy” human population is difficult. As most studies enrolled disproportionately many young patients, it is questionable whether results can be translated to more vulnerable depressed populations (e.g. elderly, patients with cardiovascular impairments) [47].

Other uses of ketamine with moderate level of evidence

(1) In pediatrics:
(a) As premedication: It can be administered by the oral (5–8 mg/kg), intramuscular (4–6 mg/kg), or iv (1–2 mg/kg) routes. The advantages include its analgesic properties and the ability to cause sedation without respiratory depression [48]. Because of its rapid onset of action, ketamine has been used as an IM induction drug in children and difficult to manage mentally retarded patients [49]. Intranasal ketamine is these days widely studied for procedural sedation, a recent publication reviewed 11 studies and suggests that intranasal ketamine at doses up to 10 mg/kg appear to be safe in children with adequate analgesia at doses as low as 0.5 mg/kg. They also concluded that the most common adverse effect of intranasal ketamine was vomiting, reported in 10 studies at doses of at least 1 mg/kg. Although studies on children suggested that adequate sedation can be achieved safely with intranasal route, however evidence is limited and its overall quality of evidence is low necessitating the need for larger high quality trials [50]. It is used for sedation or general anesthesia for pediatric procedures like cardiac catheterization, radiation therapy, radiological studies such as magnetic resonance imaging, dressing changes, and dental work [51]. Combination of low doses of ketamine and propofol provides effective and safe sedation-analgesia in pediatric emergency short surgical procedures and in adults undergoing colonoscopy and short gynecological procedures [52-54].

(b) Caudal epidural block: A quantitative systematic review of randomized controlled trials on adding ketamine to pediatric caudal anesthesia concluded that ketamine prolonged analgesia with few side effects compared with local anesthetic alone [55]. Another meta-analysis stated that caudal ketamine in pediatric patients was associated with decreased post-operative pain and non-opioid analgesic requirements [56]. In 2018, Sharon PA et al compared postoperative analgesic effect of caudal bupivacaine with and without ketamine in pediatric sub-umbilical surgeries and found that caudal administration of ketamine 0.5 mg/kg along with 0.75 ml/kg
0.25% bupivacaine significantly prolongs the duration of postoperative analgesia in children more than plain bupivacaine without any significant adverse reactions [57].

(2) **Ketamine as an adjuvant & its role to overcome the pitfalls of dexmedetomidine:**

We have been reading about adjuvants used with ketamine to averse its undesirable effects but very recently there is increasing number of evidence suggesting its utility as an adjuvant to averse pitfalls of sedatives like dexmedetomidine. In 2012, Tobias in his review has highlighted that dexmedetomidine is generally effective for sedation during noninvasive procedures but there is enough literature available suggesting that it’s not a promising choice for painful procedures as a sole agent. Pitfalls described were its long onset time, limited analgesic effect and undesirable hemodynamic perturbations like bradycardia and hypotension. Tobias categorically mentioned many robust trials where adding low dose ketamine to dexmedetomidine led to satisfactory outcomes in invasive procedures in both adults and children. He suggested that when used together, ketamine prevents bradycardia and hypotension, which has been reported with dexmedetomidine and also hastens the onset [58]. Char et al in their research paper clearly stated that dexmedetomidine alone is inadequate to provide adequate sedation for either pediatric intensive care management or procedural sedation. It also has an adverse effect on the conduction system leading to hemodynamic instability. They observed decrease in heart rate after dexmedetomidine administration which returned to baseline after co-administration of ketamine (mean difference between baseline and after ketamine 6.5 bpm; 95% CI, 11.2 to 1.8; P = 0.005) [59]. Recently in 2020, a double-blind randomized controlled study concluded that adding ketamine to dexmedetomidine had led to good postoperative analgesia, decreased postoperative opioid requirements and smooth recovery after functional endoscopic sinus surgery [60]. Sinha et al compared dexmedetomidine plus ketamine combination with dexmedetomidine alone for awake fiberoptic nasotracheal intubation and concluded that addition of low-dose ketamine (15 mg as a bolus of 5 mL,
followed by continuous infusion at 20 mg/h) further enhances the hemodynamic stability and provided better sedation than dexmedetomidine alone [61]. Kim et al [62] and Chunn et al [63] in their respective studies have found that combination of ketamine and dexmedetomidine led to shorter procedural time, improved sedation quality, hastens the onset of sedation with lesser incidences of desaturation. Qiao et al had reported lower rate of successful venous cannulation in children with dexmedetomidine alone (47%) whereas it was 80% when ketamine was added to it (p=0.006) [64].

(3) In critical care medicine: Ketamine used for patients in a critical care unit provides combined sedation and analgesia and has favorable effects on hemodynamics and can treat persistent bronchospasm. A recently published multi centric retrospective study evaluated the use of ketamine infusions in 390 adult ICU patients suggest there is no consensus regarding the indication, dose, or dose units associated with ketamine, hemodynamic changes appear common which started occurring as early as 4 hours after starting infusion, however other adverse effects appear to be minimal [65]. In 2015 Umunna BP et al also suggested that ketamine is a good sedative agent along with its low incidence of adverse effects, thus it may be a reasonable alternative for patients requiring mechanical ventilation [66]. In septic patients with cardiovascular instability, ketamine because of its cardiovascular stimulatory effects reduces inotropic support and exerts a protective anti-inflammatory effect against the sepsis process [67].

Overall there is very little research is available on its use in critical care settings, mostly its efficacy in emergency department and anesthesia practice has been extrapolated to its applicability in ICUs.

Other uses of ketamine with low level of evidence

(1) In alcohol withdrawal: Ketamine offers a plausible pharmacologic mechanism for use in the setting of severe alcohol withdrawal is that both ketamine and alcohol antagonize the NMDA receptor.
The authors of a retrospective study assessed the effect of ketamine infusion added to usual therapy with benzodiazepines titrated to symptoms on requirements for benzodiazepines in patients admitted with delirium tremens (DT) and found that rate of endotracheal intubation and mean duration of ICU stay was drastically reduced [68]. Yet another retrospective analysis noted that benzodiazepine doses drastically went down after initiation of a ketamine infusion In addition to that better symptom control was achieved with new regimen and had no adverse neurological outcomes and hemodynamic perturbations [69].

Unfortunately, very limited literature is available for ketamine use in alcohol withdrawal and all studies were retrospective, open-label studies involving simultaneous use of numerous different agents. None of these studies proves anything about the use of ketamine infusions for alcohol withdrawal.

(2) Ketamine for status epilepticus: Super refractory status epilepticus (SRSE) is defined as status epilepticus (SE) continuing after 24 hours of anesthetic infusion or recurrence after discontinuation of anesthetic infusion. Typically, SE is treated with a combination of benzodiazepines and specific antiepileptics, quickly escalating to anesthetic infusions (most commonly propofol). Prolonged SE and SRSE are associated with a downregulation of GABA-A receptors and an upregulation of NMDA receptors, nicely positioning ketamine as a therapeutic adjunct, especially given concerns for adverse effects of prolonged propofol infusions, such as hyperlipidemia and propofol infusion syndrome. There are no randomized trials comparing ketamine to other agents in SRSE. Sabharwal et al studied patients, most of whom were on both propofol and ketamine infusions, in a neurocritical care setting [70]. They concluded that 1.5 mg-10.5 mg/kg/hour is the recommended dose of ketamine infusions and should be combined with 1.5-8 mg/kg/hour dose of propofol infusion. A case audit involving several nations revealed that ketamine was considered only for the most severe cases of SE and that too late in the course of the disease [71]. More recent experience with ketamine and a possibility for a neuroprotective
effect make the case for early administration (duration of SE < 3 days) rather than late rescue [72, 73]. An Italian group reported their experience in children on a protocol that used IV ketamine for refractory SE upfront added to other antiepileptics. They found that in instances in which ketamine was used as the sole anesthetic agent for refractory SE, there was the added benefit of avoiding endotracheal intubation [74]. This experience has not been replicated in adults but is intriguing. In 2015 Sreshtha GS et al also concluded that Ketamine can be a safe, effective, readily available and economic therapeutic agent for the management of super-refractory status epilepticus in patients with hemodynamic instability [75].

Unfortunately, no RCT is available to test its safety and efficacy in status epilepticus cases. Most of the available literature is either case reports or series having low level of evidence.

Some other clinical uses of ketamine available in literature

Most of these clinical applications have just been mentioned in case reports with no randomized trials. Large multicentric studies are needed to recommend its routine use:

1. **Cardiopulmonary bypass (CPB) surgery:** A number of opportunities remain for ketamine to be studied in cardiac surgery patients. The current literature supports the idea that ketamine attenuates the inflammatory response to cardiac surgery with CPB. Whether this consistently leads to improved clinical outcomes remains unclear. It also has potential use in the postcardiac surgery ICU because of its excellent hemodynamic profile, minimal respiratory depression, and potent analgesic properties. However, at this time there is a paucity of studies to support its use in this setting. Mogahad MM et al had compared safety and efficacy of ketamine-dexmedetomidine (KD) versus ketamine-propofol (KP) combinations for sedation in patients after coronary artery bypass graft surgery and concluded that KD provided short duration of
mechanical ventilation with less fentanyl dose requirement in comparison with KP whereas hemodynamic stability and length of the ICU stay was same with both the regimens [76]. Future studies comparing ketamine to other commonly accepted sedative regiments, such as propofol and dexmedetomidine are critically needed in cardiac surgery patients [77]. Some authors have reported that a single dose of ketamine 0.5 mg/kg given upon induction was associated with lower serum levels of C-reactive protein and lower incidence of delirium and cognitive dysfunction after cardiac surgery with CPB. This is because of the neuroprotective and antiinflammatory effects of ketamine [78].

2. Electroconvulsive therapy (ECT): Given the need for anesthesisia during electroconvulsive therapy (ECT) and the excitement about ketamine's acute effects in reducing depressive symptoms, combining the two therapies seemed a logical next step. A study showed that S-ketamine given for ECT decreased the number of ECT sessions, produced lower depression severity scores and higher cognitive ratings [79]. A study showed that ketamine-propofol combination (ketofol) can be an alternative strategy to enhance the seizure quality and clinical efficiency of ECT [80, 81]. Shams and El-Masry compared Ketamine- Dexmedetomidine (KD) with Ketamine-Propofol (KP) combination in ECT procedure and concluded that KD had an effective anti-depression, less agitation and more patient satisfaction when compared to KP [82]. However, the research on ketamine use in ECT has been starkly disappointing so far [83]. The clinical enthusiasm is tempered by concerns that ketamine's antidepressant activity is short lived and by uncertainty regarding long-term safety in repeated administrations, with unknown risks for long-term cognitive side-effects, psychotic symptoms, and substance abuse [84].
3. Ketamine gargles has shown to reduce the incidence of postoperative sore throat and hoarseness of voice after endotracheal intubation in general anesthesia [85-88].

**Ketamine and emergence reactions**

Most of the anesthesiologists are apprehensive of the hallucinations, delirium and the nightmares which patient experiences while awakening and these cluster of symptoms are categorized as "reemergence phenomenon". Several receptors as well as neurochemical mechanisms have been hypothesized to be implicated in the occurrence of emergence phenomena (EP) like NMDA, opiates, dopamine, acetylcholine etc. Hence, a wide variety of drugs belonging to different class are being tried to prevent or treat symptoms of emergence phenomena with some success.

37th expert committee on drug dependence released a review report which also states that these symptoms were found to be reduced by concurrent use of benzodiazepines, putting the patient in a low stimulus environment and by providing information on the possible emergence reactions preoperatively.

A randomized controlled trial was conducted in 2011 on 200 patients who received ketamine for procedural sedation. Authors concluded that 23% of patients experienced reemergence phenomenon with ketamine whereas just 8% patients exhibit such symptoms when 0.03 mg/kg of Midazolam was given along with it [89]. Another cross sectional observational study conducted by Lohit et al also concluded that perioperative administration of midazolam with ketamine was found to be effective in controlling EP, leading to a smooth postsurgical recovery [90]. Another recent RCT published in 2019 also concluded that premedication with either midazolam 0.05 mg/kg or haloperidol 5 mg intravenously significantly reduces ketamine-induced recovery agitation while delaying recovery [91].

**Ketamine uropathy**: Ketamine uropathy (KU) describes the effects of ketamine on the urinary system. It is a misnomer to use ketamine cystitis or ketamine bladder syndrome as, whilst the bladder is often
most severely affected, the whole urinary tract may be damaged. A 2019 study from Taiwan have found that 84% of the total 106 ketamine users had shown lower urinary tract symptoms (LUTS) and in most of these cases LUTS appeared at a mean of 24 months after its daily use [92]. The largest study assessed symptoms in 1056 male users and noted a prevalence of 76%. Again, they found a significant correlation between higher age (>30 years), longer duration of use (>24 months) and co-use of other illicit drugs with symptom severity [93]. Chang T et al in their study found that moderate to severe LUTS including frequency, urgency, dysuria and hematuria when the mean daily consumption of ketamine was 3.2 ± 2.0 g and they also reported that the mean interval from consumption to the development of LUTS was 12.7 months (range, 2-36 months) [94].

Authors couldn’t find any large RCT on ketamine uropathy but all available literature clearly states that long term continuous use of ketamine (most commonly as recreational agent) leads to lower urinary tract symptoms which are mostly dose and duration dependent. However most of these symptoms are reversible after discontinuation of ketamine.

Summary: Ketamine’s role in operating room as anesthetic, sedative, amnestic and analgesia agent is well established since its discovery. Moderate level of evidence is available to prove its role in traumatic brain injury patients, acute pain services, chronic non cancer pain and as an antidepressant. Low level of evidence is available for its role in patients with raised intraocular pressure (dose <4mg/kg), cancer pain management and critical care settings. Most of its adverse reactions are minor, incidence of emergence reaction has been reported in most of the available literature but can be easily managed with concurrent use of benzodiazepines.

Till today, there are plenty trials ongoing despite its increasing addiction burden in western society. But science never feared any evil. Various policies, legislations and support groups are coming up to fight
with the addiction problems with ketamine, popular as the “super K”. In the era of evidence based medicine, the so called “Super K” can be a boon to medical science if we leave our age old fears of conquering the heights. Like every individual this drug has its good and bad. Now, the challenge is on us to find the pious and fight the evil.

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Figure 1: Structure of ketamine: The chiral center of the cyclohexanone ring results in S-(+) and R-(-) isomers.