

## Ketamine: Use in Anesthesia

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### SUMMARY

The role of ketamine anesthesia in the prehospital, emergency department and operating theater settings is not well defined. A nonsystematic review of ketamine was performed by authors from Australia, Europe, and North America. Results were discussed among authors and the final manuscript accepted. Ketamine is a useful agent for induction of anesthesia, procedural sedation, and analgesia. Its properties are appealing in many awkward clinical scenarios. Practitioners need to be cognizant of its side effects and limitations.

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## Introduction

In the last decade, ketamine has gained popularity in the prehospital, emergency department (ED) and operating theater setting; however, its role is not well defined. Ketamine is a potent dissociative analgesic and anesthetic. Proponents advocate that its properties are appealing in many awkward clinical scenarios. In this nonsystematic review, we present useful concepts based on the available literature and our clinical experience gathered in America, Australia, and Europe.

## Racemic and S-(+)-Ketamine: Differences in Effects and Dosing

Ketamine contains an asymmetrical carbon atom; this leads to two optical isomers: the S-(+) and the R-(-) isomer, which have

different pharmacologic profiles [1]. The S-(+)-isomer is two-fold more effective and longer acting than the racemic mixture of both isomers; hence, half of the dosage is required with S-(+) as compared with the racemic ketamine [2–4]. S-(+)-ketamine is available only in some countries, for example, in the European Union [5], thus if not mentioned otherwise, ketamine in this text refers to the racemic ketamine and intravenous (IV) administration.

Racemic ketamine is available in three different concentrations: 10, 50, and 100 mg/mL. The 50 mg/mL solution is commonly stocked because it can be easily injected IV and intramuscular (IM). The S-(+)-ketamine solution is preservative free, which may decrease neurotoxicity. S-(+)-ketamine is available in two formulations: 5 and 25 mg/mL [6]. The incidence of side effects is comparable at equal plasma concentrations [6], although some report fewer side effects and a shorter recovery with S-(+)-ketamine.

## Administration Routes

Ketamine is suitable for administration via multiple routes (Table 1), emphasizing its adaptability to many clinical scenarios [6]. The optimal route of administration of ketamine is IV, but this may not always be achievable, for example in emergencies; children; and obese patients [7].

Improved tools for intraosseous (IO) access have made this route of administration safe [8,9]. The onset of anesthesia is slightly later with IO as compared with IV injection (71 vs. 56 second) [10].

The IM route has been used for decades [11]. It is safe and predictable although painful to give [12–14]. Compared to IV, the IM route is associated with longer recovery times and a higher rate of vomiting [15]. Co-administered ondansetron reduces the incidence of emesis in children (number needed to treat [NNT] = 9) [16]. A similar antiemetic effect is seen with the concomitant use of propofol [17].

Oral racemic ketamine tastes bitter [6]. Recently, the first report of a lozenge containing ketamine 25 mg was published. The peak effect was delayed (15–30 min vs. 1–5 min IV), and the clinical response may be unpredictable.

Intranasal administration (IN) is facilitated by the large surface, uniform temperature, high permeability, and extensive vascularization of the nasal mucosa. This results in a rapid systemic absorption. These properties combined with the ease of access make this route appealing [18]. A high inter-individual peak-plasma concentration, likely to be due to swallowing and drug draining out of the nose, results in a variable effect [19,20]. On rectal administration, peak-serum concentrations are reached after 40 min [21–23].

## Prehospital Applications of Ketamine

An ideal anesthetic agent for prehospital care would induce anesthesia rapidly and predictably while maintaining homeostasis

**Table 1** Route of administration, bioavailability, and the starting dose of ketamine

Route of administration	Bioavailability	Starting dose
Intravenous	100%	0.25–1 mg/kg (adults)* 0.25–2 mg/kg (children)* 1–2 mg/kg <sup>†</sup>
Intraosseous	100% [141,142]	0.5–1 mg/kg* 1–2 mg/kg <sup>†</sup>
Intramuscular	93% [143]	4–5 mg/kg* [144] 8–10 mg/kg <sup>†</sup> [144]
Oral	16–20% [145,146]	Children: 3–15 mg/kg* [6,145] Adults: 500 mg max.* [6]
Nasal	45–50% [143,147]	0.25–4 mg/kg * [19,20,57] 3–9 mg/kg <sup>†</sup> [19,20,57]
Rectal	25–30% [147]	50 mg* 8–15 mg/kg <sup>†</sup> [22,23,143,147]

Note that ketamine should be titrated to the required clinical effect. \*Analgesic and sedation dose. <sup>†</sup>Anesthetic dose.

(cardiovascular stability, maintenance of respiratory reflexes) [24]. In addition, a wide therapeutic range, potent analgesic effects at sub-anesthetic doses, and stable physicochemical properties in a variety of environmental conditions make the drug very attractive for prehospital analgesia. Ketamine, with its unique properties, versatility and perceived safety margin, makes it an appealing therapeutic option for prehospital and in hospital practitioners [25]. However, its uniqueness also induces clinical and logistical considerations that must be considered separately from its use in the hospital context.

## Prehospital Anesthesia Induction

Prehospital intubation is undertaken in a less controlled environment than in hospital. The overall success of rapid sequence induction (RSI) is dependent on the appropriate selection of induction and neuromuscular blocking agents to provide optimal intubation conditions [24,26]. In addition, the safety and the process of anesthesia cannot be disrupted by the prehospital conditions [27,28].

An induction dose of ketamine 1–2 mg/kg IV induces dissociative anesthesia 1–2 min after IV injection. This is longer than the arm-brain circulation time desired for “rapid” unconsciousness. In a critically ill patient, ketamine provides cardiovascular stability, because it exerts sympathomimetic action in patients with an intact autonomic nervous system, which compensates for its direct negative inotropic effect on an isolated heart [29]. Additionally, as respiration is maintained through the induction phase until the onset of neuromuscular paralysis, oxygenation may be more effectively maintained [30].

Patients in shock who require ongoing resuscitation have maximal sympathetic activity [24,26]. An induction dose reduction to 0.5–1 mg/kg may be advisable as hypotension has been described in this situation [31]. The only comparable drug in terms of hemodynamic stability is etomidate. However, adrenal function may be suppressed for >24 h even after a single administration with an associated increase in mortality in septic patients. This has reduced the appeal of etomidate and its use may be declining in some centers [32–37]. Ketofol (a mixture of ketamine and propofol) has been suggested as an alternative agent with a favorable hemodynamic profile in the hospital setting [38]. It is unclear whether it offers particular advantages to ketamine in the prehospital setting.

Ketamine is appropriate for patients with traumatic brain injury (TBI), despite initial concerns about raised intracranial pressure (ICP) due to a possible increase in cerebrospinal fluid production and rise in partial arterial carbon dioxide pressure (paCO<sub>2</sub>) [25,27,31,40]. As controlled ventilation, which is facilitated by anesthesia, is critical for control of paCO<sub>2</sub> to prevent secondary brain injury, this issue is not clinically relevant. Cerebral autoregulation may also be impaired in TBI with the result that cerebral perfusion pressure is critically dependent on mean arterial pressure. Hence, systemic hemodynamic stability becomes particularly vital [31]. In addition, ketamine’s action via NMDA receptor antagonism has been suggested to be beneficial in TBI [25,41].

## PreHospital Analgesia

The relief of pain is an essential component of prehospital care [42]. Ideal prehospital analgesia should result in the patient

experiencing pain that is no worse than mild, be able to be provided rapidly ( $\leq 10$  min) while maintaining responsiveness to verbal stimuli and avoiding major adverse events such as respiratory impairment, hemodynamic compromise, and excessive sedation [43]. Maintaining responsiveness to verbal stimulus is particularly valuable in the prehospital setting, where access to the patient may be compromised, and repeated assessment of level of consciousness may form a vital ongoing part of patient assessment and monitoring.

Prehospital analgesia is frequently suboptimal [44], perhaps due to concerns of adverse effects. Ketamine is a useful prehospital analgesic due to its ability to provide excellent analgesia similar to morphine or fentanyl, but with a lower incidence of respiratory depression, as demonstrated in fracture management [45], burns analgesia [46], and traumatic amputation [47]. Sedation and analgesia can usually be achieved with 0.25–1 mg/kg (Table 1). Ketamine may be particularly useful in a patient in whom parenteral opioids have already been administered without adequate pain relief. For example, coadministered ketamine (average 40 mg IV) and morphine (5 mg IV) are superior to morphine (mean 14 mg IV) alone in the prehospital setting [48]. This is best achieved gradually by giving incremental doses while maintaining verbal contact.

### Prehospital Procedural Sedation

Ketamine has an established role in procedural sedation in the ED, including pediatrics. Its use in disaster and limited resource situations is well recorded. Particular scenarios may arise where surgical procedures are required in the prehospital context. These include acute life-threatening situations such as managing major hemorrhage, and amputation to facilitate patient extrication. In a retrospective review, 32 patients received ketamine during the insertion of a chest drain; no relevant complications occurred [12]. When compared to alternative sedatives, the analgesia provided by ketamine is particularly valuable. Descriptions of the use of benzodiazepines alone reveal cases where administration of such an agent leaves the patient aware of the procedure without analgesia [49]. In the context of prehospital procedural sedation, it remains important to administer supplemental oxygen and provide as much patient monitoring as is practical.

### Special Circumstances

#### The Combative Patient

The combative, agitated patient requiring RSI, and tracheal intubation presents a difficult clinical scenario [50]. These patients often prevent or obstruct meaningful clinical intervention, contributing to deterioration in their clinical state. While it is essential to identify and treat any factors contributing to their agitation, gaining control of the clinical situation prior to undertaking a formal RSI is necessary. Embarking on a RSI without optimizing patient position, ensuring pre-oxygenation and good IV access makes complications much more likely [26]. When dealing with a combative trauma patient, the clinician is left with a few alternatives, for example, physical restraint or sedation with benzodiazepines, antipsychotic drugs or ketamine [51,52]. Ketamine can be

administered IM if IV access is not possible. This enables optimization of the patient before RSI. Using a single drug (e.g., IV ketamine 1–2 mg/kg; IM 8–10 mg/kg [5,6]) for this purpose simplifies the process, saving time, and decreasing drug errors.

### Patient Extrication

Ketamine is a particularly useful analgesic and sedative in the trapped patient, to whom there may be limited access. The extrication may take hours; repeated bolus doses of ketamine can allow excellent analgesia and painless extraction [52]. Alternatively, extrication may need to be expedited for a variety of reasons, and provision of analgesia may facilitate more rapid release of the patient.

### Pediatric Patients

Control of pain and stress in children who enter into the emergency medical system is a vital component of emergency care [53]. A number of barriers exist to achieving adequate pediatric analgesia; these include unwanted attention from authority figures; perceived superiority of hospital care; difficulty obtaining IV access, and a culture of low-dose administration [54]. All played important roles in an overall preference to defer pediatric analgesia [55]. Ketamine is suitable for use in pediatrics for analgesia, procedural sedation, and anesthesia. In a review of its use in 164 children seen by the London Helicopter Medical Service, ketamine was predominantly used in awake nontrapped patients with blunt trauma for procedural sedation and analgesia; no major side effects were reported [56]. The ability to administer ketamine by a number of routes also makes it a valuable tool in pediatric care. For example, IN ketamine in pediatric burns is recommended at a dose of 0.25–0.5 mg/kg (Table 1) [57].

### Disaster Medicine

Disaster medicine represents an area where the ideal qualities of ketamine as a prehospital agent are at the fore, and it has therefore been widely used as a field anesthetic in austere conditions. Experience from Banda Aceh [58], Kashmir [59], and Haiti [60] demonstrates its usefulness. Where possible, it is appealing to supplement ketamine anesthesia with regional anesthesia where there is a paucity of equipment.

In Kashmir, 149 patients received emergency surgery using ketamine anesthesia with benzodiazepine premedication. This was safe, effective, and had a low incidence of major adverse effects [59]. In Haiti, where there were many cases, sedation was frequently employed using IV midazolam (0.05–0.1 mg/kg) and ketamine (1–2 mg/kg) with augmentation with local anesthesia where possible [60]. This technique allowed the patient to remain spontaneously breathing, and reduced recovery time and staffing requirements.

### Limitations

Ketamine has a number of side effects, which can be managed adequately in the prehospital setting if anticipated and identified. For instance, emergence phenomena with ketamine have pre-

vented its widespread use in hospital practice for general anesthesia. While emergence phenomena will rarely be of significance for the prehospital practitioner, the hospital team may have to manage such reactions later during the patient's hospital care. One of ketamine's positive features is that it has minimal effect on central respiratory drive if given slowly, although rapid IV injection can cause transient apnea [6]. Ketamine increases salivary secretions, which may increase the incidence of laryngospasm. Many of these reported effects may be due to partial airway obstruction, which usually responds to simple airway maneuvers [6]. Secretions can be anticipated and some recommend to manage them with a small dose of an anticholinergic, for example atropine (0.01 mg/kg) [61].

Hypothermia is a common comorbidity during the prehospital phase. The interplay between ketamine and hypothermia is poorly researched. Ketamine is good at minimizing the fall in core temperature usually associated with anesthesia as it reduces the magnitude of redistribution hypothermia [62]. However, the sympathomimetic effects on an irritable hypothermic heart and its reduced metabolism have potential for serious side effects that have not been researched.

## Ketamine Use in the Emergency Department

Intravenous ketamine has long been a mainstay for pediatric procedural sedation in the ED [63]. More recently, there has been increasing interest in the use of ketamine for adult procedural sedation, often combined with sedatives such as propofol or midazolam [64–66].

The characteristic dissociative state seen with ketamine becomes apparent with doses of 1.0–1.5 mg/kg and is characterized by a trance-like cataleptic state in which there is potent analgesia, sedation, and amnesia. Spontaneous respirations, airway reflexes, and cardiovascular stability are maintained [67]. Absolute contraindications to IV ketamine sedation are age <3 months and schizophrenia. Relative contraindications include increased ICP, glaucoma or acute globe injury. Caution is suggested in patients with cardiovascular disease, porphyria or thyroid disorder [15].

For ED procedural sedation, a loading dose (1.5–2.0 mg/kg IV in children or 1.0 mg/kg IV in adults) administered in 30–60 second is recommended (Table 1). For shorter procedures, a single loading dose is adequate, while for longer procedures, the dissociative state can be maintained with incremental doses of 0.5–1 mg/kg [15].

Common adverse events associated with ketamine sedation include recovery agitation (1–2% in children, 10–20% in adults), muscular hypertonicity, and emesis (5–15%). Other potential adverse events such as laryngospasm and hypersalivation are rare [15,68]. Pretreatment with atropine or glycopyrrolate is no longer routinely recommended [15].

The use of ketamine and propofol mixed in a single syringe (so-called “ketofol”) has become a popular agent for ED procedural sedation as the opposing physiological effects of ketamine and propofol can be used to clinical advantage as ketamine mitigates propofol-induced hypotension, and propofol mitigates ketamine-induced vomiting and recovery agitation [69]. The drugs are

chemically compatible when mixed [70] and appear to have a synergistic effect as deep sedation is reliably achieved with half the dosage requirements of each drug alone (average 0.7 mg/kg of each drug) [71]. Two randomized controlled trials have shown improved sedation consistency with ketofol compared with propofol alone, and no difference in the incidence of adverse respiratory events [71,72]. Administering the agents in separate syringes is also commonly used for procedural sedation. In this circumstance, subdissociative ketamine is administered as an analgesic agent, with subsequent titration of sedation depth with intermittent propofol boluses of 10–40 mg every 2–3 min [73–75]. Ketamine also reduces morphine requirements in ED trauma patients [76].

## Ketamine in the Operating Theater Neurotoxicity

Ketamine provides profound analgesia after neuraxial application, which has triggered great interest in its potential benefits during neuraxial anesthesia. However, the widespread use of ketamine has been hampered due to fear of potential neurotoxicity. Animal studies showed neurotoxic effects for many local anesthetics [77], but not for ketamine in doses commonly used for regional anesthesia [78,79]. Compared with other spinal agents, for example, local anesthetics and opioids, ketamine has no life-threatening cardiovascular, neurological or respiratory side effects if administered unintentionally IV or intrathecally [78,80]. However, in human neuroblastoma cells and rat astrocytes, the combined toxicity of ketamine and lidocaine was additive [81]. In one animal study, high intrathecal ketamine (1.6 mg/kg) resulted in three dead animals of 30 [82]. Neurotoxicity was reported in a patient after long-term intrathecal administration of ketamine with preservatives due to chronic pain [83]. Preservatives may be causative of this neurotoxicity, but this is unproven. In neonatal rats, ketamine, which is a potent inducer of neural apoptosis, has a therapeutic index (i.e., toxic dose/analgesic dose) <1 [79], while the same index is >300 for morphine and clonidine [84]. Thus, a recent editorial cautioned against using ketamine in neonatal caudal blocks [85].

## Ketamine in Children Regional Anesthesia

The efficiency of caudal ketamine has been reported by several studies (Tables S1 and S2). With inguinal herniotomy, ketamine 0.5 mg/kg added to bupivacaine 0.25% as compared with plain bupivacaine 0.25% was more analgesic [86]. Also, ketamine 0.5 mg/kg as compared with clonidine 2 µg/kg or epinephrine 5 µg/kg added to bupivacaine 0.25% provided longer analgesia after orchidopexy (12.5 vs. 5.8 vs. 3.2 h) [87]. Increasing dosages of ketamine (0.25, 0.5, and 1 mg/kg) prolonged analgesia after orchidopexy (7.9 vs. 11 vs. 16.6 h) [88]. There was no difference between the groups regarding motor block, sedation, and urinary retention but slight psychogenic side effects were noted with ketamine 1 mg/kg. Thus, the most appropriate dose is likely to be 0.5 mg/kg [88]. In children undergoing orchidopexy, ketamine was added either to bupivacaine 0.125% or 0.25%; analgesia was

equivalent but motor-block regression faster with bupivacaine 0.125% (8 vs. 9.5 h) [89]. Ropivacaine 0.2% and ketamine 0.25 mg/kg provided analgesia for 12 h as compared with 3 h for plain ropivacaine 0.2% [90]. During spinal anesthesia, an IV propofol 3.2 mg/kg/h per ketamine 0.8 mg/kg/h infusion conveyed better sedation than propofol 4 mg/kg/h alone ( $n = 40$ ) [91].

Caudal anesthesia with S-(+)-ketamine 0.5 and 1 mg/kg was comparable to bupivacaine 0.25% with epinephrine 1:200,000 ( $300 \pm 96$  min vs.  $273 \pm 123$  min vs.  $203 \pm 117$  min) [92]. After inguinal hernia repair, S-(+)-ketamine produced 8.8 h analgesia, as compared with 1.8 h with IM ketamine [93]. After subumbilical surgery, the addition of S-(+)-ketamine 0.5 mg/kg as compared with clonidine 2  $\mu$ g/kg to ropivacaine 0.2% or plain ropivacaine had a longer analgesic effect (11.7 vs. 8.2 vs. 4.8 h) [94]. Similarly, after such surgery, S-(+)-ketamine 0.5 mg/kg with ropivacaine 0.1% prolonged analgesia compared to plain ropivacaine [94]. S-(+)-ketamine 1 mg/kg plus clonidine 1  $\mu$ g/kg also prolonged analgesia as compared with S-(+)-ketamine 1 mg/kg alone [95].

A recent quantitative systematic review of randomized controlled trials on adding ketamine to pediatric caudal anesthesia concluded that ketamine prolonged analgesia compared with a local anesthetic alone (mean difference 5.6 h) with few side effects, although uncertainties over neurotoxicity still need to be clarified [96]. Another meta-analysis stated that caudal ketamine in pediatrics was associated with decreased postoperative pain and nonopioid analgesic requirement. However, ketamine failed to exhibit an opioid-sparing effect [97].

## General Anesthesia

After tonsillectomy ( $n = 60$ ), ketamine 0.5 mg/kg added to fentanyl 1 mg/kg improved analgesia without delaying hospital discharge [98]. Also, ketamine 0.5 mg/kg added to anesthesia induction with sevoflurane 5% and alfentanil 10  $\mu$ g/kg ( $n = 50$ ) improved intubation conditions in spontaneously breathing children while preserving hemodynamic stability [99]. Similarly, in children with congenital heart disease ( $n = 50$ ), hemodynamics were better preserved and adverse respiratory effects were fewer and milder after anesthesia induction with IM ketamine 5 mg/kg as compared with sevoflurane 3% [100]. Hemodynamics were also better preserved in oncology children ( $n = 47$ ) undergoing procedural anesthesia with ketamine 0.5 mg/kg and propofol 0.5 mg/kg as compared with propofol 1 mg/kg [101]. Successful anesthesia was reported for MRI with a multidrug approach consisting of midazolam, ketamine, and propofol [102].

Ketamine 0.25 mg/kg but not propofol 1 mg/kg attenuated sevoflurane-induced postoperative agitation ( $n = 60$ ) [103]. Less agitation as compared to saline was also reported by two other studies [104,105].

## Ketamine in Adults

### Regional Anesthesia

After cesarean section ( $n = 188$ ), 10 mg IV ketamine supplementing spinal bupivacaine, fentanyl, and morphine, and IV ketorolac had no additional postoperative analgesic benefit [106], while

S-(+)-ketamine 0.05 mg/kg compared with fentanyl 25  $\mu$ g added to 10 mg bupivacaine 0.5% enhanced the segmental spread and shortened the duration of analgesia [107]. In women undergoing spinal anesthesia during brachytherapy for cervix carcinoma ( $n = 60$ ) with either bupivacaine 10 mg or bupivacaine, 7.5 mg plus ketamine 25 mg analgesia was comparable but duration of motor block and requirement of fluids were less in the ketamine group. However, more patients complained of psychomimetic effects and nausea and vomiting in this group [108]. When comparing spinal anesthesia for transurethral prostatectomy ( $n = 40$ ) with bupivacaine 10 mg or bupivacaine 7.5 mg plus S-(+)-ketamine 0.1 mg/kg onset of motor and sensory block were shorter in the bupivacaine plus S-(+)-ketamine group [109]. In patients ( $n = 40$ ) assigned to a sedation of propofol (1.5 mg/kg/h) vs. propofol-ketamine (1.2 mg/kg/h and 0.3 mg/kg/h) during spinal anesthesia, the latter conveyed more hemodynamic stability [110]. Ketamine sedation 0.5 mg/kg/h during spinal anesthesia for arthroscopic knee surgery attenuated ischemia-reperfusion markers ( $n = 30$ ) [111]. Remifentanyl-induced postoperative hyperalgesia may be prevented by ketamine 0.5 mg/kg at incision followed by 5  $\mu$ g/kg/h until skin closure and 2  $\mu$ g/kg/h for 48 h [112].

## General Anesthesia

S-(+)-ketamine (1–3 mg/kg bolus, followed by 2–4 mg/kg/h) during elective coronary-artery-bypass graft (CABG) surgery exerts antiinflammatory effects during and after cardiopulmonary bypass ( $n = 128$ ) [113]. Hemodynamics are also improved and antiinflammatory effects were evident in cardiac surgery patients ( $n = 50$ ) with ketamine 0.25 and 0.5 mg/kg as compared to placebo [114]. No antiinflammatory effects were seen after single-dose administration of ketamine 0.5 mg/kg after CABG-off-pump surgery ( $n = 50$ ) [115]. A systematic review concluded that intraoperative ketamine exerts antiinflammatory effects [116]. In hemodynamically stable elective CABG-patients ( $n = 209$ ), S-(+)-ketamine did not accentuate postoperative troponin-T rises, and hemodynamic function was comparable [117]. Propofol co-induction with 0.5 mg/kg ketamine compared with propofol alone may be propofol sparing, resulting in less hemodynamic depression; this may be advantageous in hemodynamically unstable or fragile patients [118,119].

Propofol (1.5 mg/kg) plus ketamine (0.8 mg/kg) provided better anesthesia in patients with depressive disorders undergoing electroconvulsive therapy [120]. No postoperative beneficial analgesia was conveyed after cesarian section ( $n = 140$ ) when ketamine 0.25–1 mg/kg was added during anesthesia induction [121]. Similarly, anesthesia with propofol/ketamine vs. propofol/alfentanil for dilatation and curettage ( $n = 60$ ) was comparable but the ketamine group required more time before orientation returned [122]. After thoracotomy ( $n = 49$ ), ketamine 0.05 mg/kg/h, as compared to saline, added to epidural ropivacaine and morphine provided better analgesia [123]. Similarly, epidural as compared with IM ketamine (1 mg/kg in both groups,  $n = 60$ ) reduced intra- and postoperative analgesia requirement [124].

After cholecystectomy ( $n = 120$ ), ketamine 2 mg/kg subcutaneously infiltrated vs. 1 mg/kg IV 15 min before surgery provided better analgesia for 24 h [125]. Ketamine 0.5 mg/kg on induction

followed by 10 µg/kg/h until wound closure decreases perioperative opiate requirements in opiate-dependent patients with chronic back pain undergoing back surgery (n = 102) [126]. Perioperative ketamine 0.15 mg/kg, as compared with saline, reduced pain in women undergoing laparoscopic surgery (n = 135) [127].

## Psychogenic Effects

Ketamine has been recognized as a potent psychedelic drug and dissociative anesthetic since its introduction into clinical practice. It provokes imaginative, dissociative states, and psychotic symptoms up to schizophrenia due to its NMDA-antagonistic action [128–130] as well as severely impairing semantic and episodic memory when used in sub-anesthetic doses [130]. A dissociative effect of *loss-of-self*, inability to move the body, and isolation of mind from body is reported when ketamine is used as a sedative or analgesic. These are acute effects; little is known of the longer-term sequelae [131]. Used as an anesthetic, ketamine can cause emergence phenomena. These have been variously described as a floating sensation, vivid pleasant dreams, nightmares, hallucinations, and delirium. The phenomena are more common in >16 year, in females, in shorter operative procedures, and those receiving large doses particularly when these are administered quickly [40,63]. Intravenous ketamine in healthy volunteers (n = 40) without premedication resulted in more mental abnormalities than thiopentone, these changes were not present by the following day [132]. Benzodiazepines effectively prevent these phenomena. Midazolam is particularly favoured and has been shown to reduce the incidence of unpleasant dreams when compared with diazepam (NNT = 6) [65,133]. Propofol and various other benzodiazepines such as lorazepam, diazepam, flunitrazepam are effective but the latter can delay recovery [134]. Benzodiazepines are not coadministered regularly with ketamine. For example, in a case series, midazolam was coadministered only to 12 of 32 patients (38%) [42,135]. A recent trial (n = 100) reported that a positive persuasion may reduce unpleasant sensations [136].

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In children, mild emergence reactions can happen up to 15 days after ketamine [137]. Dose is important. For example, no more nightmares than in controls were described in children (n = 90) after 0.5 mg/kg ketamine [138] but after a dose of 7 mg/kg 7.1% described them. In 301 children given ketamine 0.5–2.5 mg/kg with midazolam, the incidence of bad dreams was ~1.7% after the first postoperative night [139]. In adults, no psychological effects have been reported with subanesthetic doses (0.1 mg/kg); however, at 0.5 mg/kg, some anxiety and paranoia have been reported [129]. Unpleasant dreams seem to be due to the diminishing positive effect of positive emotions rather than intensification of negative emotions [140]. Despite these sequelae, ketamine is regaining popularity as a sedative, analgesic, and anesthetic agent.

## Conclusions

Ketamine is a useful agent for induction of anesthesia, procedural sedation, and analgesia. Its properties are appealing in many awkward clinical scenarios. Practitioners need to be cognizant of its side effects and limitations.

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## Conflict of Interest

The authors declare no conflict of interest.

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## Supporting Information

The following supplementary material is available for this article:

**Table S1.** Prolongation of postoperative analgesia with caudal ketamine in pediatric patients, adapted from [80].

**Table S2.** Prolongation of postoperative analgesia with caudal S-(+)-ketamine in pediatric patients.