

Clinical Practice Guideline for Emergency Department Ketamine Dissociative Sedation: 2011 Update

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We update an evidence-based clinical practice guideline for the administration of the dissociative agent ketamine for emergency department procedural sedation and analgesia. Substantial new research warrants revision of the widely disseminated 2004 guideline, particularly with respect to contraindications, age recommendations, potential neurotoxicity, and the role of coadministered anticholinergics and benzodiazepines. We critically discuss indications, contraindications, personnel requirements, monitoring, dosing, coadministered medications, recovery issues, and future research questions for ketamine dissociative sedation. [Ann Emerg Med. 2011;57:449-461.]

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INTRODUCTION

The dissociative agent ketamine has been the single most popular agent to facilitate painful emergency department (ED) procedures in children for nearly 2 decades.¹⁻³ Current ketamine protocols, including indications, contraindications, and dosing, are frequently based on a widely cited 2004 clinical practice guideline,¹ which in turn was an update of a 1990 protocol.⁴ This latter article was cited in 1999 as an "example of compliance" by The Joint Commission.⁵ The 2004 guideline, however, is now substantially out of date and in need of revision because subsequent ketamine investigations have questioned, disproved, or refined several of its assertions and recommendations. During this same period, there has also been sufficient ED research in adults to support expansion of ketamine use beyond children. In addition, animal research describing neurotoxicity with ketamine raises important new questions that must be considered and further investigated in humans.

To describe the best available evidence and perspectives about optimal dissociative sedation practice, we reviewed the newer ketamine literature and updated the 2004 clinical practice guideline.

WHY A SEPARATE CLINICAL PRACTICE GUIDELINE FOR KETAMINE?

Emergency physicians already have access to various standards,⁶ policies,⁷ guidelines,^{8,9} and review articles^{10,11} dealing with the general practice of procedural sedation and analgesia. However, ketamine displays unique features that warrant considering it separately from other sedatives.

The underlying pharmacology of ketamine is fundamentally different from that of other procedural sedation and analgesia agents. This drug exerts its effect by "disconnecting" the

thalamocortical and limbic systems, effectively dissociating the central nervous system from outside stimuli (eg, pain, sight, sound). The resulting trance-like cataleptic state of "sensory isolation"¹² is characterized by potent analgesia, sedation, and amnesia while maintaining cardiovascular stability and preserving spontaneous respirations and protective airway reflexes.^{4,12-16} Complete analgesia permits performance of extremely painful procedures.

Rather than displaying the dose-response continuum observed with all other procedural sedation and analgesia agents, ketamine dissociation appears at a dosing threshold of approximately 1.0 to 1.5 mg/kg intravenously (IV) or 3 to 4 mg/kg intramuscularly (IM). In smaller doses, ketamine exhibits analgesia and disorientation. Once the dissociative threshold is reached, administration of additional ketamine does not enhance or deepen sedation, as would be the case with opioids, sedative-hypnotics, or inhalational agents.^{4,17} For these other agents, the more drug administered, the more the patient progresses along the sedation continuum, with increasing probability of ventilatory depression. In contrast, the quantity of ketamine administered has no clinically important effect on airway integrity and respirations within the range of clinically administered doses and using standard administration methods.^{2-4,14,17-20} Accordingly, dissociative sedation can be readily achieved by administration of a single IV or IM loading dose, and the only need for titration, in contrast to other sedatives, is to maintain the dissociative state over time.

This unique mechanism of action has made it challenging to reconcile ketamine with the traditional stages of the sedation continuum.¹⁷ Dissociated patients are unable to respond to external stimuli (including repeated or painful stimulation), and

thus this sedated state is inconsistent with traditional definitions of “moderate sedation” or “deep sedation.”^{6,8,9} This nonresponsiveness has led some to label it “general anesthesia”; however, this definition is also incompatible with ketamine because it specifies that “the ability to independently maintain ventilatory function is often impaired” and that “patients often require assistance in maintaining a patent airway.”^{6,8,9} Ketamine-related airway and respiratory adverse events are rare rather than “often,” and thus lumping the drug into this category unfairly suggests an exaggerated level of risk.

The optimal resolution to such confusion is the application of a separate definition altogether, as has been advocated by the American College of Emergency Physicians: “A trancelike cataleptic state characterized by profound analgesia and amnesia, with retention of protective airway reflexes, spontaneous respirations, and cardiopulmonary stability,” ie, dissociative sedation.^{1,7,10,17} When others attempt to fit ketamine into one of the traditional sedation continuum states, they should recognize its technical incompatibility with that definition. Ultimately, semantic debates over what to call ketamine serve little purpose. It is more important to appreciate that ketamine is fundamentally distinct pharmacologically from general anesthetic agents and other procedural sedation and analgesia agents.^{4,17}

MATERIALS AND METHODS

We assembled a clinical practice guideline update committee of 4 senior ketamine researchers, including the 2 authors of the previous version. We limited our panel to emergency physicians because the ED is the exclusive focus of this guideline, emergency physicians have a widely accepted leadership role in procedural sedation and analgesia,^{10,11,21} and emergency physicians have a natural reluctance to permit other specialists to dictate emergency medical practice.²²

To perform this update, we searched MEDLINE from January 2003 to November 2010, using the single search term “ketamine,” manually searched the tables of contents of the leading emergency medicine and anesthesiology journals during the same period, and searched the reference lists of all identified articles for additional relevant articles. Pertinent resulting articles were reviewed by the committee, and their merits were debated by e-mail and during a group meeting on September 12, 2010.

We graded the availability and strength of scientific evidence from the medical literature, using descriptive terms adapted from the American Society of Anesthesiologists⁹:

- **Supportive:** There is sufficient quantitative information from adequately designed studies to describe a compelling relationship between a clinical intervention and a clinical outcome.
- **Suggestive:** There is enough information from case reports and descriptive studies to provide a directional assessment of the relationship between a clinical intervention and a clinical outcome.
- **Inconclusive:** Published studies are available, but they cannot be used to assess the relation between a clinical intervention and a clinical outcome because the studies do not provide a clear causal interpretation of findings or because of research design or analytic concerns.

- **Insufficient:** There are too few published studies to investigate a relationship between a clinical intervention and clinical outcome.
- **Silent:** No studies that address a relationship of interest were found in the available published literature.

EXPLANATION OF CLINICAL PRACTICE GUIDELINE CONTENT

The updated clinical practice guideline is shown in Figure 1, with major changes from the previous version summarized in Figure 2. The following is explanatory information and evidence in support of its sequential elements. A general approach to ketamine dissociative sedation is shown in Figure 3.

Objective

To provide evidence-based recommendations for use of ketamine dissociative sedation in the ED.

Definition of Dissociative Sedation

This recommended^{7,10} definition has been crafted according to the unique features of the dissociative state.^{4,12,15-17}

Characteristics of the Ketamine “Dissociative State”

Detailed descriptions of the unique clinical manifestations of ketamine are beyond the scope of this guideline, and interested readers are referred to other sources.^{4,12,15,16,23}

Indications

The literature is strongly supportive of the safety and efficacy of ED dissociative sedation for a variety of brief painful or emotionally disturbing procedures in both children^{2,3} and adults,²⁴⁻²⁸ eg, fracture reduction, laceration repair, abscess drainage. Dissociative sedation is useful for procedures in the mentally disabled, who are often uncooperative.^{29,30}

Ketamine may also be safely used for longer procedures,^{2-4,12,15,16} although patients in whom prolonged intervention is anticipated may be more optimally treated with other agents or in other settings. For procedures that require motionless sedation, such as computed tomography or magnetic resonance imaging, ketamine is less effective because of occasional random movements typical of dissociative sedation, which may result in poor-quality radiographic study results.^{11,23} Ketamine offers no advantage over pure sedative-hypnotics in this setting.

Contraindications: Absolute (Risks Essentially Always Outweigh Benefits)

Age. There are multiple anecdotal observations and reported cases of airway complications with ketamine in infants younger than 3 months, including airway obstruction, laryngospasm, and apnea.^{4,12,16,31,32} This propensity toward airway adverse events is not particular to ketamine but rather represents infant-specific differences in airway anatomy and reactivity and laryngeal excitability.^{4,12,16,33}

Mental state. Ketamine has been shown to exacerbate schizophrenia,³⁴ and this evidence suggests that other

procedural sedation and analgesia options should be used in such individuals. Although the literature is silent about ketamine and other forms of psychosis, caution is advised.

Contraindications: Relative (Risks May Outweigh Benefits)

Age. The previous guideline recommended that ketamine be avoided in children between 3 and 12 months because of anecdotal concerns about a potentially higher risk of airway complications.^{4,12} This recommendation is now omitted; a large meta-analysis failed to corroborate this concern^{2,3} and the global evidence now suggests minimal or no enhanced risk.

The previous guideline addressed only pediatric administration; however, there is now sufficient ED literature to also support the safety and efficacy of dissociative sedation in adults lacking hypertension, heart disease, or risk factors for coronary artery disease (see “Cardiac Disease” section below).^{24-28,35,36}

Laryngeal stimulation. Ketamine is well known to preserve and exaggerate protective airway reflexes,^{4,12,16} and there is supportive evidence from non-ED settings that major stimulation of the oropharynx (eg, endoscopy) during dissociative sedation will increase the risk of laryngospasm.³⁷ However, a large meta-analysis found no such increased risk for typical ED oropharyngeal procedures (eg, intraoral laceration repair, dental procedures, removal of oropharyngeal and esophageal foreign bodies).^{2,3} Clinicians using ketamine for such procedures should make every effort to avoid accumulation of secretions or blood in the posterior pharynx while avoiding vigorous stimulation of the posterior pharynx with either suction or instruments.

Anatomy. Although the existing literature is inconclusive about the suitability of ketamine in patients with a history of airway instability, tracheal surgery, tracheal stenosis, tracheomalacia, and laryngomalacia, it remains plausible that these conditions likely entail a higher risk of laryngospasm and airway obstruction.^{4,12,16}

Upper respiratory infections. According to indirect inconclusive evidence, active upper respiratory infection and active asthma appear to present increased risk in children but not adults. These features are well known to increase laryngospasm risk in children during inhalational anesthesia. Olsson and Hallen³³ found that, in children with upper respiratory infection, the risk was 5.5 times higher than in those without, and when active asthma was present the risk was 3.7 times higher. Adults did not display such differences.³³ It remains uncertain whether this predisposition observed during inhalational anesthesia applies to ketamine, although regardless of drug, presumably the laryngospastic response has similar underlying pathophysiology. Given that ketamine exaggerates laryngeal reflexes,^{4,12,16} whereas inhalational anesthetics depress them, the risk with ketamine might actually be higher in this setting.

Shortly after the release of ketamine in 1970, anecdotal associations between upper respiratory infection and laryngospasm appeared, and as a result essentially every ketamine review article or textbook chapter lists upper respiratory infection as a contraindication.^{1,4,12,15,16} There is

insufficient evidence to clarify what specific magnitude of upper respiratory infection signs and symptoms should preclude ketamine administration.

Asthma. Although ketamine has been used as therapy for active asthma,³⁸⁻⁴¹ there is insufficient experience to support its safety in this setting, and indeed asthma is a known laryngospasm risk factor in pediatric inhalational anesthesia.³³ There is no evidence to support quiescent asthma as a contraindication. Ketamine is not contraindicated for rapid sequence intubation in severe asthma, assuming that a neuromuscular blocker is coadministered to eliminate the possibility of laryngospasm.

Laryngospasm. Given that several of the relative contraindications described above are based on an enhanced risk of laryngospasm, it is expected that emergency physicians will appraise this risk according to their relative comfort with managing this adverse event. Ketamine-associated laryngospasm is relatively uncommon (0.3% incidence in children in the large meta-analysis)² and essentially always has been transient and responded quickly to assisted ventilation and oxygen. There are 2 reported occurrences of protracted and recurrent ED laryngospasm, including 1 child who required intubation⁴²; however, neither child experienced hypoxia or any complications.

Cardiac disease. According to inconclusive evidence, it has been widely recommended that ketamine be avoided in children or adults with known or possible coronary artery disease, congestive heart failure, or hypertension.^{12,15,16,43} Ketamine inhibits the reuptake of catecholamines, and the resulting sympathomimetic effect produces mild to moderate increases in blood pressure, pulse rate, cardiac output, and myocardial oxygen consumption. Evidence is inconclusive about whether the increased coronary perfusion associated with this hyperdynamic state parallels increases in oxygen demand.^{4,12,16,44,45}

The literature is silent about a maximum age for ketamine. Although this drug can precipitate myocardial ischemia in the elderly,⁴⁶ no such occurrences have been reported in the ED setting.²⁴⁻²⁸ Although millions of older adults in the developing world have safely received ketamine during the past 40 years (where this drug continues to be widely administered in operating theaters as an inexpensive and simple alternative to inhalational anesthesia^{4,31,35,36}), coronary artery disease is uncommon in such settings. Although ketamine has been used for cardiac surgery in the elderly, this has been in conjunction with cardiodepressant agents that would be expected to mitigate its effects.^{24,26} Emergency physicians must weigh the risks and benefits of ketamine in older adults who may have unrecognized coronary artery disease.

The literature is silent about any association between ketamine and over-the-counter sympathomimetics (eg, pseudoephedrine) or prescription stimulants (eg, methylphenidate), and so these medications do not represent a contraindication.

Purpose

- To define guidelines for patient selection, administration, monitoring, and recovery for ED dissociative sedation.

Definition of Dissociative Sedation

- A trancelike cataleptic state induced by the dissociative agent ketamine, characterized by profound analgesia and amnesia, with retention of protective airway reflexes, spontaneous respirations, and cardiopulmonary stability.

Characteristics of the Ketamine “Dissociative State”

- Dissociation: After administration of ketamine, the patient passes into a fugue state or trance. The eyes may remain open, but the patient does not respond.
- Catalepsy: Normal or slightly enhanced muscle tone is maintained. On occasion, the patient may move or be moved into a position that is self-maintaining. Occasional muscular clonus may be observed.
- Analgesia: Analgesia is typically substantial or complete.
- Amnesia: Total amnesia is typical.
- Maintenance of airway reflexes: Upper airway reflexes remain intact and may be slightly exaggerated. Intubation is unnecessary, but occasional repositioning of the head may be necessary for optimal airway patency. Suctioning of hypersalivation may occasionally be necessary.
- Cardiovascular stability: Blood pressure and pulse rate are not decreased and typically are mildly increased.
- Nystagmus: Nystagmus is typical.

Indications

- Short, painful procedures, especially those requiring immobilization (eg, facial laceration, burn debridement, fracture reduction, abscess incision and drainage, central line placement, tube thoracostomy).
- Examinations judged likely to produce excessive emotional disturbance (eg, pediatric sexual assault examination).

Contraindications: Absolute (Risks Essentially Always Outweigh Benefits)

- Age younger than 3 months (higher risk of airway complications)
- Known or suspected schizophrenia, even if currently stable or controlled with medications (can exacerbate condition)

Contraindications: Relative (Risks May Outweigh Benefits)

- Major procedures stimulating the posterior pharynx (eg, endoscopy) increase the risk of laryngospasm, whereas typical minor ED oropharyngeal procedures do not.
- History of airway instability, tracheal surgery, or tracheal stenosis (presumed higher risk of airway complications)
- Active pulmonary infection or disease, including upper respiratory infection or asthma (higher risk of laryngospasm)
- Known or suspected cardiovascular disease, including angina, heart failure, or hypertension (exacerbation caused by sympathomimetic properties of ketamine). Avoid ketamine in patients who are already hypertensive and in older adults with risk factors for coronary artery disease.
- Central nervous system masses, abnormalities, or hydrocephalus (increased intracranial pressure with ketamine)
- Glaucoma or acute globe injury (increased intraocular pressure with ketamine)
- Porphyria, thyroid disorder, or thyroid medication (enhanced sympathomimetic effect)

Personnel

- Dissociative sedation is a 2-person procedure, one (eg, nurse) to monitor the patient and one (eg, physician) to perform the procedure. Both must be knowledgeable about the unique characteristics of ketamine.

Pre sedation

- Perform a standard pre sedation assessment.
- Educate accompanying family about the unique characteristics of the dissociative state if they will be present during the procedure or recovery.
- Frame the dissociative encounter as a positive experience. Consider encouraging adults and older children to “plan” specific, pleasant dream topics in advance of sedation (believed to decrease unpleasant recovery reactions). Emphasize, especially to school-aged children and teenagers, that ketamine delivers sufficient analgesia, so there will be no pain.

Ketamine Administration: General

- Ketamine is not administered until the physician is ready to begin the procedure because onset of dissociation typically occurs rapidly.
- Ketamine is initially administered as a single IV loading dose or IM injection. There is no apparent benefit from attempts to titrate to effect.
- In settings in which IV access can be obtained with minimal upset, the IV route is preferable because recovery is faster and there is less emesis.
- The IM route is especially useful when IV access cannot be consistently obtained with minimal upset, and for patients who are uncooperative or combative (eg, the mentally disabled).
- IV access is unnecessary for children receiving IM ketamine. Because unpleasant recovery reactions are more common in adults, IV access is desirable in these patients to permit rapid treatment of these reactions, should they occur.

Ketamine Administration: IV Route

- Administer a loading dose of 1.5 to 2.0 mg/kg IV in children or 1.0 mg/kg IV in adults, with this dose administered during 30 to 60 seconds. More rapid administration produces high central nervous system levels and has been associated with respiratory depression or apnea.
- Additional incremental doses of ketamine may be administered (0.5 to 1.0 mg/kg) if initial sedation is inadequate or if repeated doses are necessary to accomplish a longer procedure.

Figure 1. Clinical practice guideline for ED dissociative sedation with ketamine.

Ketamine Administration: IM Route

- Administer ketamine 4 to 5 mg/kg IM in children; the IV route is preferred for adults.
- Repeat ketamine dose (full or half dose IM) if sedation is inadequate after 5 to 10 minutes (unusual) or if additional doses are required.

Route of Administration	IV	IM
Advantages	Ease of repeated dosing; less vomiting, slightly faster recovery	No IV access necessary
Peak concentrations and clinical onset, min	1	5
Typical duration of effective dissociation, min	5-10	20-30
Typical time from dose to discharge, min	50-110	60-140

Coadministered Medications

- Prophylactic anticholinergics are no longer recommended.
- Prophylactic benzodiazepines are no longer recommended for children; however, they should be available to treat rare, unpleasant recovery reactions, should they occur. Prophylactic midazolam 0.03 mg/kg IV may be considered for adults (number needed to benefit=6).
- Prophylactic ondansetron can slightly reduce the rate of vomiting (number needed to benefit=9 or more).

Procedure

- Adjunctive physical immobilization may be occasionally needed to control random motion.
- Adjunctive local anesthetic is usually unnecessary when a dissociative dose is used.
- Suction equipment, oxygen, a bag-valve-mask, and age-appropriate equipment for advanced airway management should be immediately available. Supplemental oxygen is not mandatory but may be used when capnography is used to monitor ventilation.

Interactive Monitoring

- Close observation of airway and respirations by an experienced health care professional is mandatory until recovery well established.
- Drapes should be positioned so that airway and chest motion can be visualized at all times.
- Occasional repositioning of the head or suctioning of the anterior pharynx may be indicated for optimal airway patency.

Mechanical Monitoring

- Maintain continuous monitoring (eg, pulse oximetry, cardiac monitoring, capnography) until recovery is well established.
- Pulse and respiratory rate should all be recorded periodically throughout the procedure. Blood pressure measurements after the initial value are generally unnecessary because ketamine stimulates catecholamine release and does not depress the cardiovascular system in healthy patients.

Potential Adverse Effects

(Percentage estimates are for children; corresponding adult estimates are not yet reliable enough to report.)

- Airway misalignment requiring repositioning of head (occasional)
- Transient laryngospasm (0.3%)
- Transient apnea or respiratory depression (0.8%)
- Hypersalivation (rare)
- Emesis, usually well into recovery (8.4%)
- Recovery agitation (mild in 6.3%, clinically important in 1.4%)
- Muscular hypertonicity and random, purposeless movements (common)
- Clonus, hiccupping, or short-lived nonallergic rash of face and neck

Recovery

- Maintain minimal physical contact or other sensory disturbance.
- Maintain a quiet area with dim lighting, if possible.
- Advise parents or caretakers not to stimulate patient prematurely.

Discharge Criteria

- Return to pretreatment level of verbalization and awareness
- Return to pretreatment level of purposeful neuromuscular activity
- PredischARGE requirement of tolerating oral fluids or being able to ambulate independently not required or recommended after dissociative sedation

Discharge Instructions

- Nothing by mouth for approximately 2 hours
- Careful family observation and no independent ambulation for approximately 2 hours

Figure 1. Continued.

Increased intracranial pressure. In this update, head trauma has been removed as a relative contraindication to ketamine while retaining the previous concerns relating to central nervous system masses, abnormalities, or hydrocephalus.

Repeated reports that ketamine can increase intracranial pressure^{4,12,16,47-50} have prompted traditional caution against

use of this drug in any setting of real or potential neurological compromise,^{1,4,12,16} and there are case reports of deterioration in patients with hydrocephalus.^{51,52} However, newer suggestive evidence indicates that in most patients the resulting pressure increases are minimal, assuming normal ventilation,^{51,53-55} and that ketamine's corresponding cerebral vasodilatory effect may

General

- Expansion of guideline to include adults

No Longer Contraindications

- Administration for ages 3 to 12 months
- Minor oropharyngeal procedures
- Head trauma

Route of Administration

- Emphasis on IV over IM route when feasible

Coadministered Medications

- Routine prophylactic anticholinergics no longer recommended
- Routine prophylactic benzodiazepines may benefit adults but not children
- Prophylactic ondansetron can slightly reduce vomiting

Figure 2. Major changes in the 2011 guideline.

actually improve overall cerebral perfusion.^{54,56} Given the absence of any supportive or suggestive evidence that ketamine presents a danger to the acutely traumatized brain, the historical contraindication seems overreaching.^{54,56} However, alternative agents would still appear preferable in patients with known structural barriers to normal cerebrospinal fluid flow.

Seizure disorder. Ketamine demonstrates anticonvulsant properties,^{4,12,16} and the literature is silent about any enhanced risk with underlying seizure disorder.

Increased intraocular pressure. Dissociative sedation may represent risk in patients with acute globe injury or glaucoma, given inconclusive and conflicting evidence of increased intraocular pressure with ketamine.⁵⁷⁻⁶¹

Porphyria and thyroid disease. There are anecdotal reports of enhanced sympathomimetic responses in patients with porphyria,^{62,63} thyroid disorder,⁶⁴ or thyroid medication,⁶⁴ and according to this inconclusive evidence, ketamine should be used with caution in these settings.

Fasting state. There is insufficient evidence to recommend a specific fasting duration before dissociative sedation. Despite 40 years of continual worldwide use, there are no documented reports of clinically significant ketamine-associated aspiration, except in ill neonates.^{4,12,16,65,66} A systematic review found no apparent association of fasting state with emesis, laryngospasm, or any other complication,⁴ and large, prospective ED series have also failed to show any association between fasting and adverse effects.⁶⁷⁻⁶⁹

A case-by-case risk-benefit assessment is more consistent with the current literature than setting an arbitrary fasting period.⁶⁶ Indeed, given its unique protection of airway reflexes, ketamine would appear preferable to alternative sedatives when fasting is incomplete.^{65,66}

Comorbidity. Regardless of age, patients with underlying illness are widely regarded as having a greater risk of adverse events with benzodiazepines, opioids, propofol, and inhalational anesthetics.⁸⁻¹¹ Such an association has not been similarly observed with dissociative sedation in children.^{2,3,20,70} Indeed, the

cardiopulmonary support characteristics of ketamine would appear to make this agent preferable to other procedural sedation and analgesia agents in children with substantial underlying illness.^{2-4,20,37,70} The literature is insufficient to similarly recommend ketamine over other agents in adults with underlying illness.

Personnel

There is a compelling rationale to support continuous observation by a dedicated health care professional until recovery is well established.^{2-4,68} Dissociated patients may spontaneously move their heads, and their airways may require repositioning for optimal patency. Suctioning of emesis or hypersalivation may be required.^{2,3,19,71} Evidence supports the safety of monitoring by an ED nurse while the emergency physician performs an interruptible procedure.^{4,19,72}

There is strongly supportive evidence that emergency physicians can safely administer ketamine.^{2,3} It is reasonable to assume that all such specialists who are knowledgeable about the unique features of ketamine and whose residency or fellowship training renders them skilled at procedural sedation and analgesia, resuscitation, advanced airway management, and vascular access can be considered qualified for dissociative sedation without specific additional hospital credentialing.

Pre-sedation Assessment

Emergency physicians should perform a general pre-sedation patient assessment,^{10,11} including a screen for ketamine contraindications. Accompanying family members or guardians should be educated about expected effects and potential adverse events associated with ketamine sedation. The characteristics of the dissociative state should also be discussed, especially if they will be with the patient during the procedure or recovery.

There is inconclusive evidence that phrasing the dissociative experience in positive terms before sedation can decrease the risk of unpleasant recovery reactions,⁷³⁻⁷⁵ and it is a common (but yet-unproven) practice to encourage patients to “plan” pleasant intrasession dreams.^{74,75}

Ketamine Administration: General

Dosing and adverse events. The concepts of a continuum of sedation and dose-dependent adverse events are familiar to clinicians, given that they are characteristic of nondissociative sedatives. However, there is strongly supportive evidence that ketamine does not exhibit any such dose-related adverse events within the range of clinically administered doses using standard administration techniques.^{2-4,14,18,20,76} A large meta-analysis found no dose-related adverse events across the standard dosing range, with only unusually high IV doses (ie, initial dose ≥ 2.5 mg/kg or total dose ≥ 5.0 mg/kg) increasing the risk of vomiting and slightly increasing the risk of apnea and recovery agitation.^{2,3} Thus, there is no apparent benefit to using 1 mg/kg IV rather than 2 mg/kg IV or to using 3 mg/kg IM rather than 4 to 5

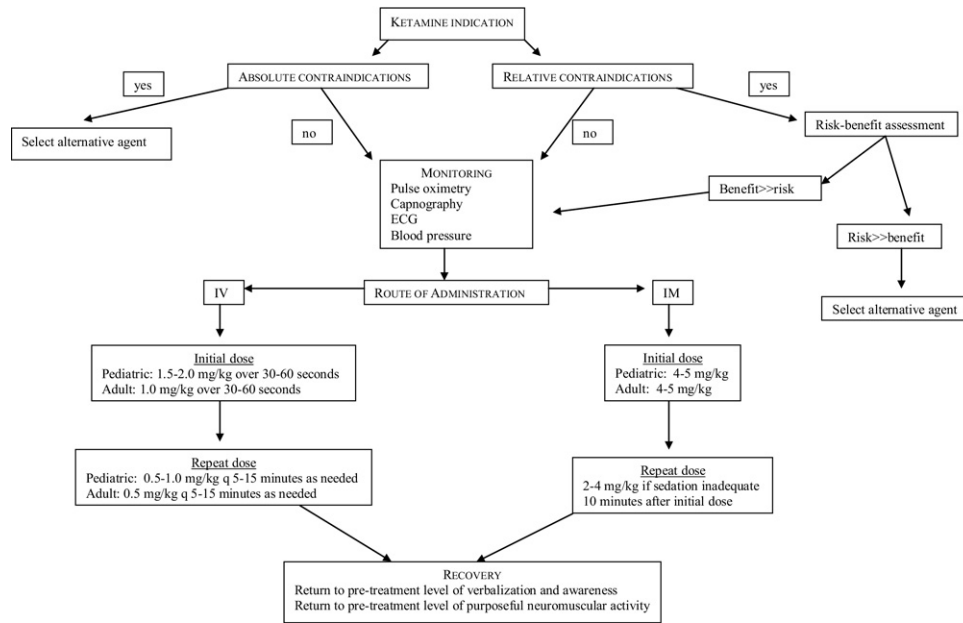


Figure 3. General approach to ketamine dissociative sedation. *IM*, Intramuscular; *IV*, intravenous.

mg/kg IM, except perhaps a slightly faster recovery with the lower dose.⁷⁷ Clinicians should consider simply using the higher dose because ketamine is less consistently effective with lower doses.¹⁸

Of historical note, during the 1970s anesthesiologists typically administered much higher ketamine doses (7 to 15 mg/kg IM) than those advocated now, and a systematic review identified no apparent difference in adverse event profiles between the higher and more standard dosing.⁴

In the large meta-analysis, subdissociative ketamine (<3 mg/kg IM) demonstrated fewer airway and respiratory adverse effects relative to full dissociative dosing; however, such low doses are inadequate for most painful procedures and showed a higher incidence of recovery agitation.^{2,3} No such association was found for IV dosing.

Route of administration. The IM and IV routes display similar risk of airway and respiratory adverse events and of clinically important recovery agitation.^{2,3,28} However, the IM route is associated with a higher rate of vomiting^{3,76} and a longer recovery,⁷⁰ and thus the literature supports preference for IV administration in settings in which venous access can be obtained rapidly with minimal upset to the child.^{2,3} The simple and inexpensive IM route may be preferable in other settings.

The IV route is also advantageous for lengthy procedures (>20 minutes) in that it permits convenient repeated dosing. IV access is also preferred for adults in the event of a clinically important unpleasant recovery reaction because occasional combativeness has been reported and midazolam can thus be promptly administered.^{36,43} Although some physicians may prefer having IV access as a precaution in case of an adverse event, the evidence strongly supports similar safety between the IV and IM routes,^{2,3,19,71,78} and there are no reported cases in

which IV access averted or would have averted an adverse outcome.^{4,12,16} However, the expertise to promptly initiate IV or, if necessary, intraosseous access should be immediately available, as is typical in the ED.

Ketamine Administration: IV Route

The minimum dose at which the dissociative state can be reliably achieved in children is 1.5 mg/kg IV, and common loading doses are 1.5 to 2.0 mg/kg.^{4,71} Repeated incremental doses of 0.5 to 1.0 mg/kg may be administered to prolong sedation. Dissociative dosing in adults is typically 1.0 mg/kg, with half doses repeated as needed.^{26,79}

Although a distinct feature of ketamine is the preservation of spontaneous respirations, the notable exception is when ketamine is administered rapidly IV. Transient respiratory depression and apnea have been reported 1 to 2 minutes after rapid IV administration, presumably from unusually high central nervous system levels.^{4,20,71} Accordingly, evidence is suggestive that IV ketamine be administered during 30 to 60 seconds.^{4,12,13,16,71} Delayed respiratory depression past the period of initial drug administration has not been reported, except when attributable to coadministered agents.

Ketamine Administration: IM Route

The minimum IM dose in children at which the dissociative state can be reliably achieved is 4 to 5 mg/kg.^{4,18,19,23} Should this initial dose result in insufficient procedural conditions, a repeated half dose or full dose is essentially always effective.^{19,23} The IM route is extremely uncommon and not preferred in adults, but similar 4 to 5 mg/kg dosing is effective.⁴

Coadministered Anticholinergics

Traditionally the prophylactic coadministration of an anticholinergic (ie, atropine or glycopyrrolate) has been routinely recommended, with the intent of mitigating oral secretions and thus presumably airway adverse events.^{1,12,15,16} However, large case series of patients have been safely treated without this adjunct.^{35,80} The large meta-analysis found anticholinergics to be associated with significantly more airway and respiratory adverse events and significantly less vomiting; however, both were at magnitudes of doubtful clinical importance.^{2,3,81} Given this lack of tangible benefit or harm, the literature is not supportive of anticholinergic prophylaxis. Instead, these drugs could be reserved for the treatment of unusual occurrences of clinically important hypersalivation or for patients with an impaired ability to mobilize secretions.

Coadministered Benzodiazepines

As with anticholinergics, the prophylactic coadministration of benzodiazepines has been traditionally recommended with the intent of preventing or reducing recovery reactions.^{4,12,15,16} A single controlled trial in ED adults found that midazolam pretreatment (0.03 mg/kg IV) significantly reduced the incidence of recovery agitation by 17% (number needed to benefit=6).²⁸ Unfortunately, this study failed to describe the nature or severity of these reactions, and so it remains unclear how many of the events were clinically important and how many were minor and transient. Nevertheless, midazolam prophylaxis appears a reasonable but nonmandatory option in adults.

In children, however, 2 controlled trials^{82,83} and a large meta-analysis³ have failed to note even a trend toward benefit from such prophylaxis. Children have far fewer recovery reactions than adults, and thus the routine pretreatment of such patients is not supported by the evidence.

When unpleasant ketamine-associated recovery reactions do rarely occur, they can be rapidly and reliably diminished with titrated benzodiazepines.^{4,12,16,19,20,36,71,83,84}

Coadministered Antiemetics

A controlled trial in ED children has shown that prophylactic ondansetron significantly decreases the rate of emesis in children by 8% (number needed to benefit=13).⁸⁵ Given this modest effect, such therapy cannot be considered mandatory. Early adolescence is the peak age for vomiting, and one option would be to target these children at highest risk for whom the number needed to benefit is 9.³ The literature is silent on antiemetic prophylaxis in adults.

Motion During the Procedure

Unlike other sedatives, ketamine does not produce muscle relaxation. Random purposeless movements unrelated to painful stimuli (including hypertonicity and clonus) may occur, and at times adjunctive physical immobilization may be needed.^{4,19,71}

Adjunctive local anesthesia is typically unnecessary for wounds and other procedures when ketamine is administered in dissociative doses.^{4,19,71}

Supplemental Oxygen

The literature strongly supports the safety of ketamine in patients breathing room air.^{4,19,72} Oxygen supplementation may delay the detection of respiratory depression by pulse oximetry^{11,86-88} and it appears best reserved for when capnography is being used to monitor ventilation.

Interactive Monitoring

The practitioner dedicated to monitoring must be prepared to occasionally reposition the head for optimal airway patency or suction the pharynx.^{4,19,71} Any sterile drapes should ideally be positioned to permit continuous visualization of the airway and chest motion.

Mechanical Monitoring

In addition to standard pulse oximetry and cardiac monitoring,^{6,10,11} capnography is being increasingly recommended during procedural sedation and analgesia because this continuous assessment of ventilation provides the earliest indication of respiratory compromise, especially central and obstructive apnea.^{88,89}

Potential Adverse Effects

The ketamine literature in children is robust enough to support fairly reliable estimates of the frequency of specific adverse events, as detailed further in this section. This is not yet possible in adults; however, their experience can be predicted to roughly parallel that of children unless contrary evidence is cited below.

In the large meta-analysis, airway or respiratory complications were observed in 3.9% of children overall, including transient laryngospasm in 0.3% and transient apnea in 0.8%.^{2,3} Misalignment of the airway may occur at any time during dissociative sedation, and stridor or hypoxemia should be initially treated with airway repositioning.^{4,19,71}

Laryngospasm. The large meta-analysis showed no association of laryngospasm with any clinical factors, except a slightly greater risk with unusually high IV doses.^{2,3,20} A case-control analysis found no association of age, dose, oropharyngeal procedure, underlying physical illness, route, or coadministered anticholinergics.⁹⁰ As discussed in the "Contraindications" section, upper respiratory infection and active pulmonary disease (including asthma) have been considered risk factors for laryngospasm according to extrapolation from inhalational anesthesia research.^{4,12,16,33,91}

Ketamine-associated laryngospasm is rare (0.3% in a large meta-analysis²), and the evidence supports it as largely idiosyncratic. However, clinicians administering ketamine must be prepared to rapidly identify and manage this adverse event. Although some patients may require bag-valve-mask ventilation,

tracheal intubation because of ketamine-associated laryngospasm is rare.^{4,42}

Respiratory depression. Respiratory depression and apnea are unusual with ketamine and are transient when they do occur. Although most commonly associated with rapid IV administration, they can rarely occur with the IM route. When respiratory depression is noticed, it is invariably at the time of peak central nervous system levels (ie, 1 to 2 minutes after IV administration or 4 to 5 minutes after IM administration).^{4,12,13,16,19,20,71}

Emesis. Early adolescence is the peak age for vomiting, with lesser risk in younger and older children.³ The literature supports it as being more frequent with the IM route compared with IV^{3,78} and supports no evidence of a dose relationship within the usual range of clinically administered doses.^{3,75} When emesis occurs, it is typically late during the recovery phase when the patient is alert and can clear the airway without assistance.^{19,72} Vomiting does occur in some patients after discharge, including some who do not vomit in the ED.^{78,83,85,92,94} The incidence of vomiting in adults can be expected to be 5% to 15%.²⁶

Recovery reactions. The ability of ketamine to induce hallucinatory reactions—both pleasant and unpleasant—during recovery is legendary. Although these so-called emergence reactions are rarely disturbing in children (1.4% incidence of reactions judged clinically important in the large meta-analysis),³ their incidence in adults varies widely (0% to 30%).^{4,12,16} The ED experience thus far is that such recovery reactions are uncommon and generally mild in adults²⁴⁻²⁸; however, clinicians should be aware of the rare potential for pronounced reactions, including nightmares, delirium, excitation, and physical combativeness.^{4,12,16,36,38,43} Titrated benzodiazepines appear to rapidly and consistently diminish such reactions.^{4,12,16,19,20,36,71,83,84} Transient diplopia as a result of rotary nystagmus is common during recovery, and transient blindness has been reported.⁹⁵

In the large meta-analysis in children, recovery agitation was not related to age, dose, or other factors to any clinically important degree, except a higher incidence in patients receiving subdissociative (<3 mg/kg IM) dosing.³ In contrast to traditional thinking, adolescents were not at substantially higher risk.^{3,94}

Recovery agitation without an apparent hallucinatory component after dissociative sedation is not uncommon. Given that it occurs at a frequency similar to that of midazolam alone,^{92,96,97} such agitation appears to be a separate entity from the ketamine-induced hallucinatory reactions.⁸² It has been associated with the degree of preprocedural agitation but not the degree of external stimulation during recovery.⁸² In one study, emergency physicians graded the severity of ketamine recovery agitation with a 100-mm visual analog scale, and the median rating was 5 mm, ie, a magnitude of minimal clinical importance.⁸²

Delayed effects. Vomiting is common in the hours after ED discharge.^{78,83,85,92,93} The evidence is insufficient to support anecdotal reports of delayed psychopathological effects or personality changes.^{4,82,98}

Recovery

Inconclusive anecdotal evidence suggests that excessive noise or stimulation during recovery from ketamine can provoke or exacerbate recovery reactions.^{4,12,16} However, one ED study found no correlation between recovery agitation and the degree of external stimulation in children.⁸² When feasible, consider recovery in a well-monitored location with muted lighting, noise, and physical contact.

Discharge Criteria

There is insufficient evidence for specific minimum discharge criteria after dissociative sedation. Given that delayed serious adverse events after ED ketamine administration have not been reported, this would be difficult to study. Typical recommendations include a return to pretreatment level of verbalization, awareness, and purposeful neuromuscular activity.⁵ One study has shown that important adverse events did not occur 30 minutes beyond final drug administration in children sedated with either ketamine or midazolam.⁹⁹

The evidence is insufficient to support a pre-discharge requirement of tolerating oral fluids after dissociative sedation, and such attempts might unnecessarily provoke emesis. Similarly, patients need not be able to ambulate without assistance after dissociative sedation.

Discharge Instructions

After receiving ketamine, patients can experience ataxia for hours, and close family observation is warranted to prevent falls.^{4,12,16} Oral intake should be delayed for a discrete period after discharge because of potential emesis.

FUTURE RESEARCH QUESTIONS

The ED ketamine literature in children is robust, with few major issues remaining unstudied. Although larger, multicenter studies would always be welcome, there is already a strong evidentiary basis in place for indications, dosing, route, and adjunctive medications and for the safety of this drug in the ED.

The high-priority study questions at this time are as follows.

Adult Use

Although the existing evidence is supportive of the safety and efficacy of ED dissociative sedation in adults, it will take larger and more focused studies to approach the rigor of what is known in children. For what indications might ketamine be preferred to other sedatives? Can we better define the adverse event profile of ketamine in adults and identify any predictors of such events? What are the optimal strategies for mitigating hallucinatory dysphoria during recovery? Is there an upper age

limit beyond which ketamine imposes undue cardiac risk?
When can ketamine induce myocardial ischemia?

Ketamine Versus Propofol

Many emergency physicians are increasingly administering propofol in settings in which they would have previously used ketamine. Propofol has fewer contraindications than ketamine and exhibits rapid recoveries generally free of recovery agitation or vomiting. Does propofol possess a safety profile sufficient to ultimately replace ketamine in most situations?

Ketamine and Propofol Combined

Several ED studies now describe the combined use of ketamine and propofol as safe and effective.^{77,100-102} But does this offer clinically important advantages over either drug alone, propofol in particular?

Subdissociative Ketamine

Some emergency physicians administer ketamine in lower doses that produce analgesia, disorientation, and obtundation rather than dissociation either because the procedure does not require such dissociation or because satisfactory conditions can be achieved with adjunctive local anesthesia or physical immobilization.¹⁰³ Faster recovery should be expected with such lower dosing. Further research is needed to identify what ED indications are appropriate for such dosing and to quantify the relative advantages and disadvantages of dissociative versus subdissociative dosing.

In other settings, ketamine has been administered in doses below the dissociative threshold to achieve pure analgesia and to reduce opioid use.¹⁰⁴⁻¹⁰⁸ A strategy of "preemptive" ketamine may decrease postoperative opioid requirements beyond ketamine's duration of effect.¹⁰⁵ It remains unclear whether any such benefits might be observed in the ED setting or whether such low-dose ketamine offers any advantages over traditional opioids for these indications.

Neurotoxicity

Rodent and monkey research strongly supports the observation that ketamine can induce accelerated programmed nerve cell death (apoptosis) when administered in high doses or for prolonged periods. Concern about potential human neurotoxicity has prompted ongoing investigations by the Food and Drug Administration and National Institutes of Health, with consideration given to removing ketamine from the market or substantially restricting it.¹⁰⁹

Although it is beyond dispute that ketamine can induce neuronal death in rodents and other animals, the literature is silent about such an effect in humans. Indeed, such a premise is at complete odds with the wealth of human experience with this agent. This animal research indicates that the minimum single dose of ketamine required to produce neuroapoptosis is 40 mg/kg, more than an order of magnitude higher than typical clinical use. This research involves animals neurodevelopmentally much

younger than the children who typically might receive ED ketamine.¹⁰⁹ Resolution of this question in humans will not be easy and will appear to require case-control studies of ED ketamine sedation with long-term neuropsychological follow-up.¹⁰⁹

Isomers

The 2 optimal isomers of ketamine, R(-) and S(+), have different properties, but the literature is inconclusive about whether this might be clinically important.^{4,12,15,16,110} The S(+) ketamine may exhibit enhanced dissociative/analgesic potency, greater amnesia, faster elimination, and fewer recovery reactions and may have neuroprotective effects.¹¹⁰ The S(+) formulation is available in Europe but not the United States or Canada.

Optimized IV Delivery

Emergency physicians typically administer IV ketamine in single or sequential doses. Although this delivery style is simple, it will frequently exceed the minimum amount of drug required. It may be possible to decrease the total amount of ketamine delivered, and thus potentially shorten recoveries, through the use of pharmacokinetic infusion models.^{111,112} Target-controlled infusion in particular has shown promise with ketamine and other drugs and deserves further study.¹¹¹

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