Clinical Practice Guideline for Emergency Department Ketamine Dissociative Sedation in Children

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We present an evidence-based clinical practice guideline for the administration of the dissociative agent ketamine for emergency department pediatric procedural sedation and analgesia. Substantial research in recent years has necessitated updates and revisions to the widely disseminated 1990 recommendations. We critically discuss indications, contraindications, personnel requirements, monitoring, dosing, coadministered medications, recovery issues, and future research questions for dissociative sedation.

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INTRODUCTION

Although largely unknown to emergency physicians before 1990,[1,2] the dissociative agent ketamine has now become one of the most popular procedural sedation and analgesia agents for children in the emergency department (ED).[3-32] Current ketamine protocols, including indications, contraindications, and dosing, are frequently based on a widely cited 1990 review article[2] in which the preexisting anesthesiology literature was summarized. In 1999, the Loma Linda University ketamine protocol based on this article was cited as an "example of compliance" by the Joint Commission on Accreditation of Healthcare Organizations (JCAHO).[33]

The 1990 review article, however, is now substantially out of date and in need of revision because subsequent ketamine investigations have questioned, disproved, or refined several of its assertions and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.[10,11,13,30,32,34,35] During this same period, there have also been substantial advances in thinking regarding procedural sedation and analgesia terminology,[36-39] appropriate presedation fasting,[40,41] sedation-related aspiration risk,[41,42] and other related aspects of general procedural sedation and analgesia practice.[36,43-45] Furthermore, in the past 10 years there has been a promulgation of clinical practice guidelines in emergency medicine and other medical specialties with the National Guideline Clearinghouse, "a public resource for evidence-based clinical practice guidelines," listing more than 1,176 guidelines on its Web site.[46] These guidelines provide a standardized, evidence-based approach to clinical decisionmaking.

To describe the best available evidence and perspectives about optimal dissociative sedation practice, we reviewed the current ketamine literature and developed an evidence-based clinical practice guideline.

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WHY A SEPARATE CLINICAL PRACTICE GUIDELINE FOR KETAMINE?

Emergency physicians already have access to various standards,[36] policies,[47] guidelines,[44,45,48] and review articles[43,49] dealing with the general practice of procedural sedation and analgesia. A central precept of these sources is that procedural sedation and analgesia agents are capable of dose-dependently inducing graded alterations in consciousness ranging anywhere along the "sedation continuum."[43] This continuum begins with "mild sedation" and, as additional medications are administered, can progress to "moderate sedation," "deep sedation," and ultimately "general anesthesia."[36,44,45,48] Implicit in the continuum principle are 2 notions: (1) to avoid dose-dependent cardiopulmonary depression, practitioners should administer the minimum amount of drug necessary to achieve the required sedation depth; and (2) achievement of this minimum sedation state is best accomplished through careful intravenous titration.

Ketamine, however, is fundamentally different from other procedural sedation and analgesia agents and is the exception to the sedation continuum tenet. Ketamine exerts its effect by "disconnecting" the thalamoneocortical and limbic systems (through simultaneous depression of the cortex and stimulation of the limbic system), effectively dissociating the central nervous system from outside stimuli (eg, pain, sight, sound). The resulting "sensory isolation"[50] of this trancelike cataleptic state is characterized by potent analgesia, sedation, and amnesia while cardiovascular stability is maintained and spontaneous respirations and protective airway reflexes are preserved.[2,17,50-52] The complete analgesia typical of the dissociative state permits extremely painful procedures to be performed that would otherwise be difficult using traditional moderate or deep sedation with benzodiazepines and opioids.[10,11,16,19,23,43]

Rather than displaying the dose-response continuum observed with all other procedural sedation and analgesia agents, ketamine dissociation is either present or absent, with a narrow transition zone. This dissociative state, once achieved, has no observable progressive depth or level, and administration of additional ketamine to an already dissociated patient does not enhance or deepen sedation, as would be the case with opioids, sedative-hypnotics, or inhalational agents.[2,38] For nondissociative agents, the more drug given, the more the patient progresses along the sedation continuum, with increasing probability of impaired independent airway function and respiratory control. In contrast, the absolute amount of ketamine given has no clinically important impact on respirations and airway integrity within the range of clinically administered doses and using standard administration methods.[2,10,34,35,38] Accordingly, dissociative sedation can be readily begun by administration of a single intravenous or intramuscular loading dose, and the only need for titration, in marked contrast to other sedatives, is to maintain the dissociative state over time.

This unique mechanism of action renders the ketamine dissociative state operationally inconsistent with the definitions of all sedation states currently promulgated by the JCAHO and American Society of Anesthesiologists.[36,37] Dissociated patients are unable to respond to external stimuli (including repeated or painful stimulation), and thus this sedated condition cannot be appropriately labeled as "moderate sedation" or "deep sedation." Ketamine does not induce general anesthesia, and the impairment of airway maintenance and spontaneous ventilation integral to this definition is not met.[36-38] Ketamine is fundamentally distinct both pharmacologically and clinically from general anesthetic agents and other procedural sedation and analgesia agents, and the JCAHO and American Society of Anesthesiologists definitions were not crafted with ketamine as a sole agent in mind. Given this incompatibility, the clinical effects of ketamine are best served by a distinct sedation category.[2,38]

We have previously defined dissociative sedation as "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."[38] We recommend that EDs in particular and hospitals in general add this definition to their JCAHO-mandated sedation policies.

EXPLANATION OF CLINICAL PRACTICE GUIDELINE CONTENT

To follow is explanatory information and evidence in support of sequential elements of the appended clinical practice guideline (Appendix), and a general approach to ketamine dissociative sedation is shown in the Figure.

Objective

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

Definition of Dissociative Sedation

This definition has been crafted according to the unique features of the dissociative state.[2,38,50-52]

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.[1,2,50-52]

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, most typically fracture reduction and laceration repair in children.[2,10,16,23,26,29,50-52] Ketamine may also be safely used for longer procedures,[2,10,23,50-54] although patients in whom prolonged intervention is anticipated may be more optimally treated with sedative-hypnotics and opioids in the ED or general anesthesia in the operating room. Ketamine is not recommended for sedation for computed tomography or magnetic resonance imaging (see section on increased intracranial pressure) because the dissociative state offers no advantage over pure sedative-hypnotics in this setting, and the occasional random movements typical of dissociative sedation may result in poor-quality radiographic studies.[1,43] Dissociative sedation has been reported as useful in uncooperative mentally disabled adults.[55,56]

Contraindications: Absolute (Risks Essentially Always Outweigh Benefits)

Age. The literature is replete with anecdotal observations and reported cases of airway complications with ketamine in infants younger than 3 months, including airway obstruction, laryngospasm, and apnea.[2,50,51,57,58] This propensity toward airway adverse events is not peculiar to ketamine but rather represents infant-specific differences in airway anatomy and reactivity, and laryngeal excitability.[2,50,51,59] Neonates and young infants requiring painful procedures are more appropriately treated with sedative-hypnotics and opioids in the ED or with general anesthesia in the operating room.

Mental state. Ketamine has been shown to exacerbate established psychosis,[60] and other procedural sedation and analgesia options should be used in such individuals.

Contraindications: Relative (Risks May Outweigh Benefits)

Age. Although historically some have recommended that ketamine be avoided in children younger than 12 months because of a presumed higher risk of airway complications,[2,50] many ED series have subsequently enrolled numerous subjects in the 3- to 12-month-old

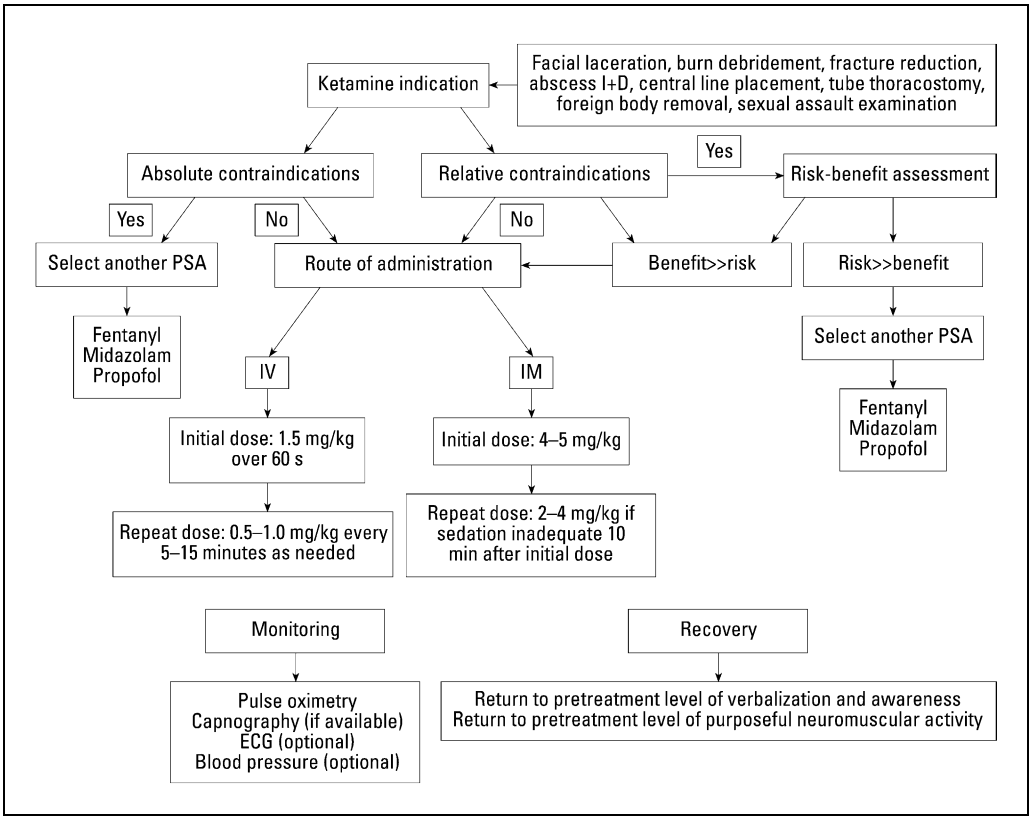

Figure.
*General approach to ketamine dissociative sedation. **I+D**, Incision and drainage; **IM**, intramuscular; **IV**, intravenous; **PSA**, procedural sedation and analgesia.*

range without resultant airway difficulties. The enhanced risk, if any, would thus appear to be minimal.[10,11,23,26]

Laryngeal stimulation. Ketamine is well known to preserve and exaggerate protective airway reflexes,[2,50,51] and there is compelling evidence that stimulation of the larynx during dissociative sedation (eg, blood from pharyngeal procedures, endoscopy) will increase the risk of laryngospasm. In a large series of ketamine for pediatric gastroenterology procedures, for example, laryngospasm was encountered in 9.4% of those undergoing upper endoscopy but in none of those undergoing colonoscopy.[54] Because laryngospasm occurs in only 0% to 3% of upper endoscopy patients sedated using benzodiazepines and opioids,[54] it is reasonable to assume that ketamine presents additional independent risk as a sedative choice during procedures with substantial laryngeal stimulation. Several authors have reported no airway complications using ketamine for dentistry and other intraoral procedures[18,28,31,61]; however, others have.[62,63]

Anatomy. Although the existing literature is insufficient to conclusively implicate a history of airway instability, tracheal surgery, tracheal stenosis, tracheomalacia, and laryngomalacia as contraindications to ketamine administration, it remains plausible that these conditions may entail a higher risk of laryngospasm and airway obstruction.[2]

Upper respiratory infections. There is indirect evidence to implicate active upper respiratory infection and active asthma as relative ketamine contraindications in children but not adults. Upper respiratory infection and active asthma are well known to increase laryngospasm risk in children during inhalational anesthesia. Olsson and Hallen[59] noticed that in patients 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. No such differences were noticed in adults.[59] It is uncertain whether this predisposition observed during inhalational anesthesia applies to ketamine, although presumably the laryngospastic response has similar underlying pathophysiology, regardless of drug. Because ketamine exaggerates laryngeal reflexes,[2,50,51] whereas inhalational anesthetics depress them, it could be reasonably argued that the risk with ketamine in this setting might actually be higher than that for the anesthetics.

Anecdotal association between upper respiratory infection and laryngospasm appeared in numerous reports shortly after ketamine's release in 1970, and according to these data and the inhalational anesthesia experience discussed previously, essentially every ketamine review article or textbook chapter lists upper respiratory infection as a contraindication.[2,50-52] There is no evidence to clarify what specific magnitude of upper respiratory infection signs and symptoms should preclude ketamine administration.

Asthma. Ketamine is not contraindicated in severe asthma with respiratory failure when it is coadministered with a neuromuscular blocker to facilitate rapid sequence intubation because concurrent paralysis effectively eliminates the possibility of laryngospasm. Indeed, ketamine is considered by many to be the sedative of choice in this setting because of its bronchodilatory properties.[2,64] Although ketamine has been administered to spontaneously breathing adults with active asthma,[65] there is insufficient experience to support its safety in this setting, and indeed asthma is a known risk factor for laryngospasm in inhalational anesthesia.[59] There is no evidence to support inactive asthma as a contraindication.

Laryngospasm. For the relative contraindications described above that are based on an increased potential for laryngospasm, it is expected that practitioners will weigh this risk according to their relative comfort with managing this complication. Although laryngospasm is relatively uncommon in the literature (0.4% incidence in the largest ED series),[10] essentially all ketamine-associated laryngospasm has been transient and responded quickly to assisted ventilation and oxygen. In fact, in a systematic review of all ketamine series in children before 1990, totaling 11,589 ketamine administrations, there were only 2 reported cases in which ketamine-associated laryngospasm led to intubation (0.02% incidence, 95% confidence interval 0.002% to 0.06%).[57,66] In both cases, it is unclear whether the intubation was required or rather used for anesthesiologist convenience. There is currently no evidence to suggest that practitioners skilled in dissociative sedation and advanced airway management cannot consistently manage laryngospasm without a greater-than-minimal risk of adverse outcome.

Cardiac disease. It is widely recommended according to circumstantial evidence that ketamine be avoided in patients with known or possible coronary artery disease, congestive heart failure, or hypertension.[50-52,67] Ketamine exerts sympathomimetic activity by inhibiting reuptake of catecholamines and produces mild to moderate increases in blood pressure, pulse rate, cardiac output, and myocardial oxygen consumption. It is unclear whether the increased coronary perfusion associated with this hyperdynamic state parallels increases in oxygen demand.[2,51,68-70] Although ketamine has been widely administered to

elderly patients in the developing world,[57,71] the baseline incidence of coronary artery disease in these populations is substantially lower than that in developed countries, and safety in this setting cannot be extrapolated.

Increased intracranial pressure. On the basis of inconclusive evidence, it is widely believed that ketamine elevates intracranial pressure.[2,50,51,72-75] Accordingly, central nervous system masses, abnormalities, or hydrocephalus must be assumed to present an increased risk for neurologic deterioration during dissociative sedation.[73-75] Similarly, patients with significant head injury (eg, associated with loss of consciousness, altered mental status, or emesis) must also be considered at risk. Sedation using other agents would appear preferable in most such cases unless neurologic imaging has excluded abnormality.

Seizure disorder. Seizure disorder has not been identified as a contraindication to ketamine, and indeed ketamine demonstrates anticonvulsant properties.[2,50,51]

Increased intraocular pressure. There is inconclusive and conflicting evidence of elevated intraocular pressure with ketamine.[76-80] Accordingly, dissociative sedation may represent risk in patients with glaucoma or acute globe injury.

Porphyria and thyroid disease. There is anecdotal and inconclusive evidence of enhanced sympathomimetic responses in patients with porphyria,[81,82] thyroid disorder,[83] or thyroid medication.[83] Ketamine should be used with caution in these patients.

Fasting state. There is no evidence that a specific fasting duration is necessary before dissociative sedation. Preprocedural fasting is intended to minimize the risk of pulmonary aspiration, and in 34 years of continual use, there are no documented reports of clinically significant ketamine-associated aspiration, except in ill neonates.[2,41,42,50,51] Indeed, several series from non-ED settings report no adverse effects from administering ketamine to nonfasted children,[2,7,84-87] and a systematic review of this research revealed no apparent association of fasting state with emesis, laryngospasm, or any other complication.[2] Two large, prospective ED series have also failed to shown any association between fasting and adverse effects.[29,88] The unique protection of airway reflexes with ketamine would appear to make it preferable to alternative sedatives in situations of incomplete fasting.[41,42]

A relative contraindication of a "full meal within 3 hours of procedure" has been widely used in emergency medicine for more than a decade; however, there is no specific evidence to support this recommendation.[1,2,10,33] A case-by-case risk-benefit assessment is more consistent with the current literature than setting an arbitrary fasting period.[41]

Comorbidity. Patients with underlying illness are believed to exhibit greater susceptibility to the cardiopulmonary depressant effects characteristic of nondissociative sedatives and anesthetics and accordingly are believed to be at greater risk of respiratory adverse events with these agents.[43,44,48,89] Such an association has not been similarly observed with dissociative sedation,[35,53] and indeed the cardiopulmonary support characteristic of ketamine may make this agent preferable to other procedural sedation and analgesia agents in patients with substantial underlying illness.[2,35,53,54]

Personnel

There is compelling evidence supporting the need for a dedicated health care professional to carefully observe each sedated patient until recovery is well established.[2,10,11,23] Dissociated patients may spontaneously move their heads, and their airways may require repositioning for optimal patency. Emesis and hypersalivation may require suctioning.[10,11] There is no evidence that the practitioner monitoring the patient and administering medications cannot be a registered nurse,[2,10,23] assuming that he or she is knowledgeable about the unique characteristics of ketamine.

There is ample evidence to support the safe administration of ketamine by anesthesiologists,[2,50-52] emergency physicians,[3-32,88] and pediatric intensivists.[53,90] It is reasonable to assume that all such specialists whose residency training renders them skilled at procedural sedation and analgesia, pediatric resuscitation, advanced pediatric airway management, and vascular access in children can be considered qualified for dissociative sedation without specific hospital credentialing. Although other literature suggests that administration by a variety of practitioners without these skill sets appears safe,[2,54] hospitals should carefully assess the advisability of specific training or credentialing for such practitioners.

Presedation

Physicians should perform a general presedation patient assessment,[43] including a specific review of absolute and relative ketamine contraindications. Accompanying family members or guardians should be educated about the unique characteristics of the dissociative state, especially if they will be with the patient during procedural sedation and analgesia.

Some clinicians believe that phrasing the dissociative experience in positive terms before sedation can lower the

risk of unpleasant recovery reactions,[91] and it is a common (but yet-unproven) practice to encourage patients to "plan" pleasant intrasedation dreams in advance.[13]

Ketamine Administration: General

Dosing and adverse events. Clinicians are highly accustomed to the concept of a continuum of sedation and dose-dependent adverse events with nondissociative procedural sedation and analgesia agents. However, there is no evidence that ketamine exhibits any dose-related adverse events within the range of clinically administered doses using standard administration techniques.[2,34,35] During the 1970s, the ketamine dose administered by anesthesiologists was typically 7 to 15 mg/kg intramuscularly[2] compared with 4 to 5 mg/kg intramuscularly today.[10,23,43] Adverse event profiles are similar between these reports using such different dosing ranges. There is no evidence to suggest that doses lower than in current use (ie, "subdissociative" doses) provide a decreased incidence of adverse effects or any clinical advantage, and indeed sedation is clearly less effective with lower doses.[34]

Route of administration. Ketamine may be safely and effectively administered by either the intramuscular or intravenous route,[2,10,11,43] and the choice should be based on practical considerations. Although some physicians may prefer having intravenous access as a precaution in case of an adverse event, there is no evidence to support the contention that intramuscular administration is any less safe than intravenous administration,[10,11] and there are no reported cases in which intravenous access averted or would have averted an adverse outcome.[2,50,51] However, the expertise to promptly initiate such access should be immediately available, as is typical in any ED.[2] Although recovery appears approximately 20 minutes faster after intravenous administration,[11] in the ED setting this relatively small difference will in many circumstances be of limited clinical importance. Intramuscular administration averts the cost, time, and discomfort associated with the initiation of intravenous access in a frightened child, and the duration of optimal operational conditions from a single injection alone (20 to 30 minutes) permits the completion of many common procedures. Ketamine should be administered intravenously, however, if such access is already in place for an unrelated reason, simply to spare a further injection. The intravenous route may also be advantageous for lengthy procedures (>20 minutes) in which intravenous access allows more convenient repeated dosing. A preferred strategy at some institutions is to administer the first dose intramuscularly and then painlessly initiate intravenous access for subsequent doses while the procedure is under way. Intravenous access is also preferred for adults so that midazolam can be promptly administered in the event of a clinically important unpleasant recovery reaction. Occasional combativeness in adults has been reported.[67,71]

Ketamine Administration: Intramuscular Route

The minimum dose at which the dissociative state can be reliably achieved is 4 to 5 mg/kg intramuscularly.[1,2,10,34] Should this initial dose result in insufficient procedural conditions, a repeated half dose or full dose is essentially always effective.[1,10]

Ketamine Administration: Intravenous Route

The minimum dose at which the dissociative state can be reliably achieved is 1.5 mg/kg intravenously.[2,11] Additional incremental doses of 0.5 to 1.0 mg/kg may be given to prolong sedation.

Although a remarkable feature of ketamine is the preservation of spontaneous respirations, the notable exception is when ketamine is given by rapid intravenous administration. Transient respiratory depression and apnea have been reported within 1 to 2 minutes of rapid intravenous administration, presumably from unusually high central nervous system levels.[2,11,35] Accordingly, it is widely recommended that intravenous ketamine be administered over 60 seconds.[2,11,17,50,51] Onset of respiratory depression delayed past the period of initial drug administration has not been reported, except in situations with coadministered respiratory depressant sedatives.

Coadministered Medications

Ketamine stimulates oral secretions, which in rare circumstances have led to airway compromise.[2,92] Shortly after the introduction of ketamine, anesthesiologists were quick to recommend routine prophylactic coadministration of an anticholinergic,[50-52] and this recommendation has gone unchallenged until recently. In a preliminary observational report of 297 children, Brown et al[93] reported similar hypersalivation scores between children receiving or not receiving concurrent atropine. Although publication of this full report is pending, this experience argues that anticholinergics cannot be considered mandatory with ketamine. Epstein[8] anecdotally describes no difficulty with administration of ketamine without an anticholinergic to approximately 1,100 children. If an anticholinergic is used, atropine is recommended because of its ready familiarity with ED staff; however, glycopyrrolate is an equally acceptable but not superior alternative.[94]

As with the anticholinergic recommendations, anesthesiologists reporting the early experience with ketamine were quick to recommend prophylactic coadministration of benzodiazepines, with the intent of preventing or reducing recovery reactions.[2,50-52] This is primarily based on anecdotal observations, and there have been only 2 adult blinded controlled trials in the 1970s.[95,96] Two recent blinded studies in children, however, have failed to document even a trend toward any benefit from such prophylaxis.[30,32] Given the potential for respiratory depression from added benzodiazepines,[5,32,67,71] they should be added to a ketamine regimen with caution in adults and avoided in most children. Although it has been suggested that there may be subsets of children who might benefit from concurrent benzodiazepine use,[32,97] there is no compelling evidence to suggest who such children might be. Indeed, the magnitude of observed recovery reactions is slight enough[30,32] that the basis for attempting to identify such subgroups does not appear persuasive. If benzodiazepines are coadministered, there is no evidence to support a preferred dose. Historically, 10 mg of coadministered diazepam has been used in full-sized adults,[50,51,95,96,98] a dose roughly equipotent to 3 mg of midazolam.

When ketamine is administered without prophylactic benzodiazepines and rare unpleasant recovery reactions do occur, titrated benzodiazepines appear rapidly and consistently effective in alleviating or substantially mitigating such reactions.[2,10,11,19,35]

Motion During the Procedure

Ketamine does not produce muscle relaxation, as do nondissociative sedatives; indeed, hypertonicity and clonus are not unusual. Random purposeless movements unrelated to painful stimuli may also occur, and practitioners should be prepared to provide adjunctive physical immobilization if needed.[2,10,11]

Given that the dissociative state produces complete analgesia, adjunctive local anesthesia is typically unnecessary for wounds and other procedures.[2,10,11]

Interactive Monitoring

As discussed earlier under "personnel," there is compelling evidence supporting the need for a dedicated health care professional to observe each sedated patient until recovery is well established.[2,10,23] This individual must be prepared to occasionally reposition the head for optimal airway patency or suction the pharynx.[2,10,11] Any sterile drapes should be positioned such that the airway and chest motion can be visualized at all times.

Mechanical Monitoring

Pulse oximetry. Continuous pulse oximetry effectively detects hypoxemia associated with airway complications during procedural sedation and analgesia and is universally recommended.[36,43-45,47] Although there is no evidence that continuous cardiac monitoring is beneficial in patients without underlying heart disease, such monitoring provides a simple, inexpensive, and readily available backup to pulse oximetry and is strongly recommended.[43]

Capnography. Capnography permits continuous assessment of ventilatory status and provides the earliest indication of respiratory compromise.[17,99] Potentially significant airway events—apnea (flatline waveform with no chest wall movement), upper airway obstruction (flatline waveform with chest wall movement responsive to chin lift/jaw thrust), and laryngospasm (flatline waveform with chest wall movement not responsive to chin lift/jaw thrust)—can all be immediately detected by capnography.[99,100]

Supplemental oxygen. Although routine oxygen supplementation is strongly recommended in patients receiving sedatives with a relatively high risk of respiratory depression (eg, propofol),[101] the safety of ketamine in patients breathing room air is well documented.[2,10,23] Oxygen supplementation is not harmful in and of itself; however, it may delay the detection of respiratory depression by pulse oximetry[43] and is recommended only when capnography is present. Regardless of operator preference about routine supplementation, oxygen should be immediately available should hypoxemia occur.

Potential Adverse Effects

In the largest ED series, airway complications were noticed in 1.4% of children receiving ketamine, consisting of airway misalignment (0.7%), transient laryngospasm (0.4%), and transient apnea or respiratory depression (0.3%).[10] Airway misalignment may occur at any time during dissociative sedation, and repositioning of the airway should be an immediate intervention in a dissociated patient who develops stridor or hypoxemia.[2,10,11]

Laryngospasm. Laryngospasm in ED procedural sedation and analgesia is a rare complication that appears unrelated to age, sex, underlying medical conditions, or dose in children.[35] However, procedures that stimulate the hyperactive gag reflex through either direct instrumentation or secretions appear to represent higher risk.[2,50,51,54] In a study of children undergoing gastrointestinal procedures using dissociative sedation, laryngospasm was noted in 9.5% of those receiving upper endoscopy and in 0% of those receiving colonoscopy. In an analysis of this

endoscopy subset, the sole risk factor for laryngospasm was age, with the risk being 3 times higher in preschool-aged children compared with school-aged children.[54] As discussed in the contraindications section, additional risk factors for laryngospasm (upper respiratory infection, age between 3 and 12 months, and active pulmonary disease, including asthma) have been extrapolated from large studies of inhalational anesthesia.[2,50,51,59]

Respiratory depression. Respiratory depression and apnea are unusual with ketamine and are transient when they do occur. Although most commonly associated with rapid intravenous administration, they can rarely occur with intramuscular administration. When respiratory depression is noticed, it is invariably at the time of peak central nervous system levels (ie, 1 to 2 minutes after intravenous administration or 4 to 5 minutes after intramuscular administration).[2,10,11,17,35,50,51]

Emesis. When emesis occurs, it is typically late during the recovery phase when the patient is alert and can clear the airway without assistance.[10,23] It occurs more frequently in older children (12.1% in those aged ≥5 years) compared with younger children (3.5% in those <5 years).[35]

Recovery reactions. Ketamine is legendary for its unique ability to stimulate hallucinatory reactions during recovery, which may be either pleasant or unpleasant. Although these so-called "emergence reactions" are rarely unpleasant in children (1.6% incidence of reactions judged greater than "mild"),[10] their incidence in adults is highly variable, with reported incidences ranging from 0% to 30%.[2,50,51] When ketamine is administered in adults, clinicians should be aware of the rare potential for pronounced reactions, including nightmares, delirium, excitation, and physical combativeness.[2,50,51,65,67,71] Titrated benzodiazepines appear to consistently and rapidly pacify such reactions.[2,30,50,51,71] Transient diplopia commonly occurs during emergence from dissociative sedation, and although well tolerated in toddlers, it can be disconcerting to older children.

Recovery agitation without an apparent hallucinatory component is not uncommon after dissociative sedation. It appears to be a separate entity from the ketamine-specific hallucinatory reactions[30] because it occurs at a similar frequency as with midazolam alone.[16,20,102] A recent study demonstrated that recovery agitation is not clinically significant in children.[30] Physicians graded ketamine recovery agitation using a 100-mm visual analog scale, with the median rating being 5 mm, low enough to lack clinical significance. Such mild recovery agitation occurs more frequently in younger children (22.5% in those <5 years) compared with older children (12.5% in those ≥5 years) and in those with underlying medical problems (33.3% in those with American Society of Anesthesiologists class 2 or greater compared with 17.9% in those with American Society of Anesthesiologists class 1).[35] It is associated with the degree of preprocedural agitation but not the degree of external stimulation during recovery.[30]

Age. In 1990, it was recommended that ketamine be avoided in ED children older than 10 years, under the assumption that this group would demonstrate a propensity toward unpleasant recovery reactions more similar to those of adults than to younger children.[2] Subsequently, however, ketamine has been widely administered to children between 10 and 15 years of age without adverse effects,[10,11,13,16,30,32] and there now appears to be no reason to avoid ketamine in this age group.

Delayed effects. There is no compelling evidence to support anecdotal reports of delayed psychic effects or personality changes.[2,30,103]

Recovery

A widely noted anecdotal observation with ketamine is that excessive noise or stimulation during recovery can provoke or exacerbate recovery reactions.[2,50,51] This assertion has never been subjected to a controlled trial. A recent ED study in children documented no correlation between recovery agitation and the degree of external stimulation during recovery.[30] Although evidence is insufficient to mandate it, whenever possible provide a well-monitored location with muted lighting, noise, and physical contact until wakefulness is well established.

Discharge Criteria

There exist no proven minimum discharge criteria after dissociative sedation. Indeed, this would appear impossible to study, given that delayed serious adverse events after ED ketamine sedation have not been reported. Common recommendations include a return to pretreatment level of verbalization, awareness, and purposeful neuromuscular activity.[33] Newman et al[104] have recently shown that primary adverse events did not occur 30 minutes beyond final drug administration in children sedated with either ketamine or midazolam.

Discharge Instructions

Ataxia can be pronounced during recovery from ketamine, and patients sent home should have close family observation to prevent falls.[2,50,51] Because there is a

predisposition to emesis after ketamine, it appears reasonable to delay oral intake for a discrete period after discharge.

FUTURE RESEARCH QUESTIONS

As discussed, much of the existing recommendations for ketamine administration are based on observational studies, anecdote, and extrapolation from the inhalational anesthesia experience. To continue to refine the ketamine clinical practice guideline, further research is recommended. Study questions at this time focus on 3 areas.

Age

What caveats are appropriate for administration of ketamine to adolescents and adults? Large series in these age groups are appropriate, with careful attention to the increased risk of unpleasant recovery reactions and aggravation of underlying coronary artery disease.

Side Effects

Emergency physicians' greatest concern with ketamine is laryngospasm, and research is needed to determine whether ketamine-induced laryngospasm is idiosyncratic or whether it can be predicted according to ketamine administration technique or patient features. Given the extreme rarity of laryngospasm, this will likely require a multicenter pooled analysis or a case-control study.

Further research is also needed to determine whether unpleasant recovery reactions are idiosyncratic or whether they can be predicted and prevented. As with laryngospasm, the rarity of such reactions will likely necessitate a multicenter study or case-control study.

The 2 optimal isomers of ketamine, R(−) and S(+), have different properties, and further research on the potential advantages for ED use of the S(+) isomer is needed.[2,50-52] Studies on the stereoisomer S(+) ketamine have shown clinical advantages over the R(−) and racemic forms. Ketamine is used as a racemic mixture containing equal amounts of the R(−) and S(+) stereoisomers. S(+) ketamine has enhanced dissociative/analgesic potency, greater amnesia, faster elimination, and fewer emergence reactions and may have neuroprotective effects. S(+) ketamine is currently in clinical use in Europe.

Antisialagogue Administration

Although preliminary evidence suggests that concurrent anticholinergics are unnecessary with ketamine, replication of this finding in other settings appears reasonable before a widespread change in clinical practice.

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APPENDIX.

Clinical practice guideline for emergency department dissociative sedation with ketamine.

Purpose
- To define the 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 noted.
- *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 psychosis, even if currently stable or controlled with medications (can exacerbate condition)

Contraindications: Relative (Risks May Outweigh Benefits)
- Aged 3 to 12 months (higher risk of airway complications)
- Procedures involving stimulation of the posterior pharynx (higher risk of laryngospasm)
- 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 due to sympathomimetic properties of ketamine). Avoid ketamine in patients who are already hypertensive and in older adults with risk factors for coronary artery disease.
- Head injury associated with loss of consciousness, altered mental status, or emesis (elevated intracranial pressure with ketamine)
- Central nervous system masses, abnormalities, or hydrocephalus (elevated intracranial pressure with ketamine)
- Glaucoma or acute globe injury (elevated intraocular pressure with ketamine)
- Porphyria, thyroid disorder, or thyroid medication (enhanced sympathomimetic effect)

Personnel
- Dissociative sedation is a 2-person procedure, 1 (eg, nurse) to monitor the patient and 1 (eg, physician) to perform the procedure. Both must be knowledgeable about the unique characteristics of ketamine.
- Avoid dissociative sedation when personnel are not experienced with ketamine or may not have time to perform such sedation properly.

Presedation
- Perform a standard presedation assessment
- Educate accompanying family about the unique characteristics of the dissociative state, especially 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 within 5 minutes.
- Ketamine is initially administered as a single intramuscular injection or intravenous loading dose. There is no benefit from attempts to titrate to effect.
- The intramuscular route is especially useful when intravenous access cannot be consistently obtained with minimal upset to the child and for patients who are uncooperative or combative (eg, the mentally disabled).
- Intravenous access is unnecessary for children receiving intramuscular ketamine. Because unpleasant recovery reactions are more common in adults, intravenous access is desirable in these patients to permit rapid treatment of these reactions, should they occur.

Ketamine Administration: Intramuscular Route

- Administer ketamine 4 to 5 mg/kg intramuscularly.
- Repeat ketamine dose (full or half dose intramuscularly) if sedation is inadequate after 5 to 10 minutes (unusual) or if additional doses required.

Ketamine Administration: Intravenous Route

- Administer a loading dose of 1.5 mg/kg intravenously over 60 seconds; 100 mg is a typical adult dose. More rapid administration produces high central nervous system levels and has been associated with respiratory depression.
- Additional incremental doses of ketamine may be given (0.5–1.0 mg/kg) if initial sedation is inadequate or if repeated doses are necessary to accomplish a longer procedure.

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

Coadministered Medications

- Concurrent anticholinergics have been traditionally administered with the intent of minimizing ketamine-associated hypersalivation, although recent evidence suggests that this recommendation has been overstated.
- If atropine is used, the typically recommended dose is 0.01 mg/kg (minimum 0.1 mg, maximum 0.5 mg). Atropine can either be given intravenously just before ketamine or mixed with ketamine in the same syringe for intramuscular injection.
- Glycopyrrolate is an acceptable alternative to atropine at equipotent doses; however, there is no evidence that it is more effective or in any way advantageous.
- In children, benzodiazepine coadministration does not appear to decrease unpleasant recovery reactions. However, they should be readily available to treat such rare reactions, should they occur.
- In adults, benzodiazepine prophylaxis should be considered because of the higher baseline risk of unpleasant reactions in this group and to enhance cardiovascular stability. Intravenous administration of 2 to 4 mg of midazolam slowly is an example of such pretreatment.

Procedure

- Adjunctive physical immobilization may be occasionally needed to control random motion.
- Adjunctive local anesthetic is usually unnecessary when a dissociative dose is used.

Interactive Monitoring

- Mandatory close observation of airway and respirations by an experienced health care professional until recovery well-established. *The patient is never left alone.*
- Drapes should be positioned so that airway and chest motion can be visualized at all times.
- Occasional repositioning of the head may be indicated for optimal airway patency.
- Occasional suctioning of the anterior pharynx may be necessary.

Mechanical Monitoring

- Suction equipment, oxygen, a bag-valve-mask, and age-appropriate equipment for advanced airway management should be immediately available.
- Maintain continuous pulse oximetry until recovery is well established.
- Maintain continuous cardiac monitoring until recovery is well established.
- Maintain continuous capnography, if available, 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

- Airway misalignment requiring repositioning of head (0.7%)
- Transient laryngospasm (0.4%)
- Transient apnea or respiratory depression (0.3%)
- Hypersalivation (1.7%)
- Emesis while sedated (0.8%)
- Emesis well into recovery (5.9%)
- Recovery agitation (mild in 17.6%, moderate or severe in 1.6%)
- Muscular hypertonicity and random, purposeless movements (common)
- Clonus, hiccupping, or rash

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
- A predischarge requirement of tolerating oral fluids 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