Ketamine: Pediatric Procedural Sedation In The Emergency Department

You are in the middle of a busy evening shift, and there are 2 children in the ED awaiting procedural sedation. One patient is waiting for fracture reduction by the orthopedic surgeon. The other has a complex laceration of the vermilion border of the lip. The waiting room is starting to fill up with more patients checking in at triage, and you see there are several more patients in the waiting room that may require sedation for fracture reductions, lumbar punctures, and abscess incision and drainage. You realize that time is of the essence, and you approach the 2 patients and start to plan for the safest, most-efficient, effective sedation.

Patient 1 is a 6-year-old boy with a right forearm injury sustained when he fell off a trampoline and landed on his outstretched hand. No head injury is reported. The examination is notable for an angulated deformity of his right forearm which is confirmed on x-rays as a midshaft radius and ulnar fracture, but no findings are suggestive of intracranial or intracranial injuries. This child is in significant pain, and his parents are urging that some medication be given. He last ate 4 hours ago and last had liquid 2 hours ago. He has a history of mild intermittent asthma but with no recent exacerbations or hospitalizations. The patient has no prior surgeries, sedations, or known drug allergies.

- What sedative agent would be the most efficient and effective (from start to recovery) for this patient?
- What are the contraindications?
- Would giving narcotics for analgesia lead to complications during his later sedation?

Patient 2 is a 12-year-old girl with a complex laceration of the vermilion border of the lip. The waiting room is starting to fill up with more patients checking in at triage, and you see there are several more patients in the waiting room that may require sedation for fracture reductions, lumbar punctures, and abscess incision and drainage. You realize that time is of the essence, and you approach the 2 patients and start to plan for the safest, most-efficient, effective sedation.

The examination is notable for an angulated deformity of his right forearm which is confirmed on x-rays as a midshaft radius and ulnar fracture, but no findings are suggestive of intracranial or intracranial injuries. This child is in significant pain, and his parents are urging that some medication be given. He last ate 4 hours ago and last had liquid 2 hours ago. He has a history of mild intermittent asthma but with no recent exacerbations or hospitalizations. The patient has no prior surgeries, sedations, or known drug allergies.

- What sedative agent would be the most efficient and effective (from start to recovery) for this patient?
- What are the contraindications?
- Would giving narcotics for analgesia lead to complications during his later sedation?
Patient 2 is a 2-year-old girl with a complex (jagged and deep) laceration through the vermilion border of her lower lip, sustained when she tripped and fell, cutting her lip on the edge of a coffee table. There was no loss of consciousness and no dental trauma. She last ate and drank 2 hours ago. Past medical and surgical history is noncontributory. The family is requesting that a plastic surgeon perform the repair, and Plastic Surgery requests that procedural sedation be used during laceration repairs.

- Is it safe to perform procedural sedation on a patient who has been 2 hours NPO for both solids and liquids?
- Should atropine be used in conjunction with ketamine to limit excessive salivary secretions during the procedure?
- Should this patient be considered as having a head injury and would this be a contraindication to ketamine use in this patient?

It is not uncommon for pediatric patients who have sustained injuries to be scared and in pain when they present to the Emergency Department (ED). Children often find it difficult to hold still or cooperate for painful and invasive procedures required to evaluate and treat their injuries because of their developmental stage. Procedural sedation has now become an integral part of the ED clinician’s practice because it is necessary to correctly and safely position the patient, provide analgesia, and limit distress.

Sedation is often required to facilitate patient cooperation during imaging studies or during painful procedures such as fracture reductions, abscess incision and drainage, lumbar puncture, or complex laceration repairs. Parents and clinicians wish to avoid causing excessive pain or distress to the child. The clinician’s need to provide compassionate care is combined with the need to deliver both safe and efficient care. The ideal sedative agent should have a favorable safety profile, be quick and easy to administer, be easily reversible, provide an adequate length and depth of sedation, and result in a relatively quick recovery to baseline.

Over the past 2 to 3 decades, several agents, used either alone or in combination, have met many of these specific requirements. Ketamine has emerged as one of the more commonly used agents in community and academic EDs both in the United States and abroad. The reasons for this include its ease of use, brief onset and duration of action, and relative low rate of cardiopulmonary complications, as well as its ability to provide both analgesia and sedation for pediatric patients.

Several organizations, most notably the American Academy of Pediatrics (AAP) and the American College of Emergency Physicians (ACEP), have published policy statements and practice guidelines outlining the requirements for practicing safe pediatric procedural sedation in an ED. (See Table 1.) In particular, ACEP’s policy statement takes a critical look at the existing literature to draw conclusions about the safe and effective use of ketamine and other sedative medications in ED settings. In addition to these guidelines, Green and Krauss published an evidence-based clinical practice guideline specifically for ketamine and its use in pediatric procedural sedation.11

This issue of Pediatric Emergency Medicine Practice takes a critical look at the recent literature on the safe and effective use of ketamine for pediatric procedural sedation in the ED. Specifically, this review will focus on safety and efficacy when ketamine is used either as a single agent or in conjunction with other medications for procedures commonly performed in the ED setting. We will also cover ketamine’s commonly cited indications and contraindications as well as the commonly reported adverse events associated with its use and how to manage these complications. Finally, we will discuss some of the current controversies that surround ketamine and its new and future applications, particularly in the prehospital setting. We’ll briefly touch on the future directions of research regarding ketamine use in the ED setting.

Critical Appraisal Of The Literature

An extensive literature search was performed in the PubMed database using multiple combinations of the search terms ketamine, procedural sedation, pediatrics, emergency department, and side effects. Those articles relevant to the practice of emergency medicine were selected, reviewed, and included in the bibliography, as were citations that appeared in review articles, clinical practice guidelines, and policy statements. Over 500 articles were reviewed, 108 of which are cited herein. Because the use of ketamine in pediatric emergency medicine has increased substantially over the past 20 years, emphasis was placed on reviewing reports and studies from 1990 to the present.
Ketamine Characteristics

Early History And Use Of Ketamine

Ketamine, formerly known as investigational drug CI-581 and now marketed as Ketalar®, is a phencyclidine derivative, first isolated in 1962 by Dr. Calvin Stevens for Parke, Davis and Company.12 Its discovery was fueled by research efforts to replace phencyclidine with a compound that had equivalent analgesic and sedative effects but fewer psychotropic effects (eg, delirium, hallucinations, confusion). Ketamine is classified as a dissociative anesthetic with potent analgesic and sedative effects. Unlike most sedative medications, it does not exhibit the typical dose–response continuum (ie, once the dissociative state is reached, administering more ketamine does not result in deeper, more profound sedation).11 Unlike narcotics and benzodiazepines, there is no known agent that can be used to reverse ketamine’s effects.

Because of ketamine’s sedative and analgesic properties and ease of administration, with minimal cardiopulmonary side effects, this drug has been used extensively in veterinary medicine. It is also a recreational drug of abuse. The most commonly noted side effects include emesis, emergence reactions, laryngospasm, apnea, respiratory depression, nystagmus, muscle rigidity, tachycardia, hypertension, and a transient erythematous upper-torso rash.13 In earlier case series and reports, ketamine use was associated with increased intraocular and intracranial pressure.14-17 However, some recent studies on anesthetized patients have called into question these “established” side effects.11,18-22

After its discovery, subsequent investigations of ketamine and its use in humans began to appear in the literature in the late 1960s and early 1970s.23-30 As its use became more common both for veterinary indications and in clinical anesthesia, studies elucidating appropriate dosing regimens and various administration routes were reported. The now widely accepted regimen for providing adequate sedation and analgesia in the majority of patients who require procedural sedation in the ED is an initial dose of 0.5 to 2.0 mg/kg of ketamine, followed by incremental doses of 0.5 to 1.0 mg/kg intravenously (IV) or 4.0 to 5.0 mg/kg intramuscularly (IM), followed by additional 2 to 4 mg/kg IM incremental dosing as needed.31,32 Although this dosing schedule achieves adequate levels of sedation for a significant majority of patients, several studies also note that increasing clearance occurs with decreasing age, necessitating more repeat dosing in the younger patient.31,32 To maintain anesthesia during prolonged procedures, a 1-mg/kg bolus of ketamine can be followed by a continuous infusion at a dose of 10 to 20 mcg/kg/min.36 Numerous subsequent studies have since concluded that ketamine can be safely used in the ED when administered by a clinician who can competently recognize and manage acute airway compromise and when the appropriate monitoring equipment is available.15,7,35,37-48

Routes Of Administration

A number of articles have compared the efficacy and benefits of IM versus IV ketamine.41-43,49-52 The most notable study was a prospective, randomized, controlled trial comparing these 2 routes in patients with orthopedic injuries who presented to a tertiary care pediatric ED.50 The study involved 208 patients given either 1 mg/kg IV or 4 mg/kg IM of ketamine. Adverse events (ie, apnea, laryngospasm, desaturations < 90%, and vomiting), efficacy of sedation, and recovery time between the two groups were compared. Although there was no significant difference in the rates of adverse respiratory events, patients who received IM ketamine had an increased rate of emesis. The other major finding was a statistically significant difference in the length of sedation (ie, between the time of ketamine administration and the time when discharge criteria were met)—129 minutes with IM ketamine versus 80 minutes with IV ketamine. The authors concluded that IV ketamine is similar to IM ketamine in terms of efficacy and safety, but IV ketamine results in a faster recovery time.

Table 1. Requirements For Safe Pediatric Procedural Sedation in The ED

<table>
<thead>
<tr>
<th>Year</th>
<th>Policy or Guideline</th>
<th>Reference</th>
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<tbody>
<tr>
<td>2006</td>
<td>Guidelines for Monitoring and Management of Pediatric Patients During and After Sedation for Diagnostic and Therapeutic Procedures: An Update</td>
<td>Coté et al, American Academy of Pediatrics4</td>
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<tr>
<td>2004</td>
<td>Clinical Policy: Evidence-Based Approach to Pharmacologic Agents Used in Pediatric Sedation and Analgesia in the Emergency Department</td>
<td>Mace et al, American College of Emergency Physicians10</td>
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<tr>
<td>2004</td>
<td>Clinical Practice Guideline for Emergency Department Ketamine Dissociative Sedation in Children</td>
<td>Green and Krauss11</td>
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Ketamine Versus Other Sedative Agents
Multiple studies have compared the efficacy of ketamine with that of other agents used for procedural sedation in the pediatric ED setting. The combination of ketamine/midazolam appears to fare favorably when compared with other agents such as fentanyl/midazolam or propofol/fentanyl. In one prospective study, Kennedy et al compared ketamine/midazolam and fentanyl/midazolam, with efficacy being the primary outcome measure. Results were recorded by blinded observers who watched videotapes of the sedation and assessed the findings with the use of the Observational Scale of Behavioral Distress—Revised (OSBD-r). Parental satisfaction, fracture reduction success rates, adverse effects, and length of sedation were also recorded. Subjects in the ketamine/midazolam group had lower OSBD-r scores (ie, less distress), less parental anxiety, and less respiratory depression but more emesis after sedation and a longer period of sedation.

Similarly, Godambe et al compared ketamine/midazolam versus propofol/fentanyl using the same OSBD-r scale. The stated primary outcomes were no difference in recovery time between the 2 regimens and no difference in procedure-related distress. While the propofol/fentanyl combination was associated with shorter recovery times (and shorter total sedation times), it was also associated with significantly higher procedure-related stress scores (although the clinical significance of this difference is most likely negligible). Both groups had similar fracture reduction success rates.

Both these studies highlight the benefit of ketamine in terms of its ability to minimize procedure-related distress and the relatively low number of adverse respiratory events. Conversely, the drawbacks of ketamine include a relatively longer recovery time and increased incidence of post sedation emesis.

Complications, Side Effects, And Safety
As mentioned earlier, some of ketamine’s well-documented complications and side effects include emergence reactions, post sedation nausea and emesis, and excessive salivary secretions leading to adverse respiratory events. Recent articles have focused on attempting to improve the safety and efficacy of ketamine by identifying risk factors for complications in certain populations or decreasing some of these known side effects. These studies investigated the benefit of adding other medications, such as midazolam (to decrease the occurrence of emergence reaction), atropine or glycopyrrolate (to decrease salivary secretions), or ondansetron (to decrease post sedation emesis). They also studied using smaller doses of ketamine to produce similar sedative and analgesic effects and combining lower doses of ketamine with other agents (eg, propofol) to shorten the time to recovery.

Indications And Contraindications
Ketamine’s unique ability to provide rapid and reliable sedation, analgesia, and amnesia, with minimal respiratory or cardiovascular compromise, makes it an ideal agent for a majority of procedures performed in the pediatric ED. Ketamine has been used for short and usually painful procedures during which the patient needs to be immobilized. (See Table 2.)

The anesthesiology literature is replete with instances of ketamine used as an adjunct to other anesthetic agents for minor obstetric, gastroenterologic, and cardiothoracic procedures, as well as for postoperative pain management. A discussion of these indications is beyond the scope of this review. In contrast, while ketamine can be used for radiological studies such as computed tomography (CT) or magnetic resonance imaging (MRI), it may not be the agent of choice in these situations because of the hypertonicity and semi-purposeful movements often exhibited by patients who have received ketamine. Furthermore, procedures such as CTs or MRIs are typically not painful and therefore do not require the analgesic properties of ketamine. In these situations, clinicians might be better served using agents that will sedate the patient and thus prevent the patient from moving but do not necessarily provide any analgesia. Agents such as propofol or pentobarbital have been used with great effect for such procedures.

Contraindications to ketamine can be divided into 2 categories: absolute and relative. Two commonly cited absolute contraindications are age under 3 months and history of overt psychosis. The absolute contraindication recommendation for infants under the age of 3 is due to the increased risk of airway compromise in this infant population as well as recent animal studies implicating ketamine in neuronal degeneration within the developing brain. While there are several studies in the literature that have looked at the safety and efficacy of ketamine in ventilated neonates undergoing cardiac catheterization and other minor surgical procedures,

Table 2. Common ED Uses For Ketamine

<table>
<thead>
<tr>
<th>In the ED</th>
<th>Other Indications</th>
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<tr>
<td>Lacerations</td>
<td>Genitourinary examination under anesthesia</td>
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<tr>
<td>Reduction of orthopedic fractures and dislocations</td>
<td>Paraphimosis reduction</td>
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<tr>
<td>Abscess incision and drainage</td>
<td>Foreign body removal</td>
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<td>Lumbar puncture</td>
<td>Tube thoracostomy</td>
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<tr>
<td>Bone marrow aspiration</td>
<td>Prehospital extrication procedures or analgesia</td>
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<tr>
<td>Dental procedures</td>
<td>Rapid-sequence intubation</td>
</tr>
<tr>
<td>Central line placement</td>
<td>Treatment of status asthmaticus</td>
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</table>
there is still a lack of studies that elucidate what effect ketamine has on the immature brain. For these reasons, ketamine use in children less than 3 months should be approached with caution. Similarly, ketamine has been shown to exacerbate psychosis in adult patients with underlying psychiatric disease. Relative contraindications cited in the literature include procedures that involve stimulation of the posterior oropharynx (increasing the risk of precipitating laryngospasm); underlying cardiovascular disease, such as poorly controlled hypertension, unstable angina or coronary artery disease, and heart failure (since ketamine’s sympathomimetic properties can lead to myocardial infarction or exacerbate heart failure); a history of porphyria or thyroid disorders (since, again, its sympathomimetic properties can exacerbate underlying disease); and age between 3 months and 12 months.

The more controversial and hotly debated relative contraindication to ketamine involves patients with head injuries who have increased intracranial pressure or altered cerebrospinal fluid (CSF) dynamics (eg, intracranial mass, hydrocephalus) and increased intraocular pressure or acute globe injury. Both of these relative contraindications are derived from early studies in which increased intracranial and intraocular pressures were noted in patients who were given ketamine, but more recent studies may belie this conclusion. (See Increased Intracranial And Intraocular Pressures section on page 6.)

Finally, as with other sedative agents, any history of severe reactions to ketamine or airway instability or tracheal anomalies also represent relative contraindications to the use of this drug because of the obvious increased risk of adverse reactions.

**Emergence Reactions**

Emergence reactions (also known as recovery reactions or emergence delirium) are a well-documented side effect of ketamine procedural sedation. The constellation of symptoms typically described in emergence reactions includes increased agitation or restlessness, dysphoria or euphoria, active dreaming or nightmares, and overt hallucinations. In a large meta-analysis that included 8282 pediatric patients, 7.6% of patients had recovery reactions (1.4% of which were deemed to be clinically important). In comparison, the incidence of emergence reactions in similar studies in adults has been reported to be as high as 30%, leading to fear about the frequent use of ketamine in the adult population. Other risk factors for emergence reactions include age > 16 years, female gender, larger doses of ketamine (≥ 2 mg/kg IV), and rapid IV administration (≥ 40 mg/min). Benzodiazepines (initially diazepam, but more recently midazolam) have been used in titrated increments to control emergence reactions when they occur. Multiple studies have looked at the co-administration of midazolam and ketamine, but based on 2 randomized, controlled trials, this approach appears to add no benefit in preventing emergence reactions. The previously mentioned meta-analysis also showed no apparent decrease in post sedation emergence reactions with adjunctive midazolam. It did show that adding midazolam increased the risk of adverse respiratory events (primarily apnea) and, conversely, decreased the risk of post sedation emesis.

A few early studies reported that emergence reactions can be diminished by decreasing the amount of environmental stimuli before ketamine induction and/or during recovery from ketamine sedation. To date, however, no controlled studies have shown that low-stimulation environments after sedation are beneficial in preventing emergence reactions. One recent study in adults included a psychologic intervention whereby patients who were to receive ketamine were interviewed in the preoperative area and were assured that the medication was safe and would provide complete analgesia during the procedure. Patients were told that the anesthetic medication would allow them to dream about a topic of their choice and were instructed to concentrate on that pleasant thought/dream during induction of anesthesia. They were also encouraged to share their thoughts and feelings before undergoing ketamine sedation. Ambient operating room and recovery room stimuli was also minimized (eg, surgeons and nurses were asked to whisper in the OR and recovery room, with minimal entering and disruption by OR staff). After the procedure, none of the patients reported unpleasant hallucinations or reactions, and all said they would be willing to receive the anesthetic agent again.

**Excessive Salivation**

Another of ketamine’s known side effects is increased salivation. Excessive salivary secretion poses a potential risk for aspiration in the moderately or deeply sedated patient. Anticholinergics such as atropine or glycopyrrolate have long been used in conjunction with ketamine in hopes of decreasing this unwanted side effect. Three studies have looked at this question. The largest study was by Green et al who carried out a large, observational, multi-center meta-analysis involving 8282 patients. This study compared the risk of adverse respiratory events when ketamine was co-administered with atropine, when ketamine was co-administered with glycopyrrolate, and when ketamine was administered alone. Green et al concluded that there was no difference in the odds of experiencing adverse respiratory events such as laryngospasm or apnea among those who received ketamine in conjunction with anticholinergics versus those who did not. In addition, a surprising finding was that ketamine...
with glycopyrrolate was associated with worse adverse airway and respiratory events (ie, desaturations < 90%, upper airway obstruction that responded to positioning) than ketamine with atropine or ketamine with no co-administered anticholinergic. Ketamine with glycopyrrolate was associated with worse periprocedural emesis than ketamine with atropine. Although anticholinergics did not reduce the risk of adverse respiratory events, studies by both Heinz et al and Green et al also showed less-frequent post procedural emesis with the addition of atropine, suggesting an antiemetic benefit with atropine co-administration.

Thus, the literature appears to suggest that atropine (and/or glycopyrrolate) does not reduce the occurrence of hypersalivation-associated adverse airway events and need not be routinely used in conjunction with ketamine sedation. However, in procedures in which control of oral secretions might be important, such as lip/tongue laceration repairs, peritonsillar abscess incision and drainage, dental extraction, and the like, one might consider the anti-salivary (as well as the antiemetic) benefits of adding atropine to ketamine in these specific cases.

Low-Dose Ketamine With Propofol

In attempts to maximize the benefits of ketamine (fast onset, potent analgesia and sedative properties, and lack of hemodynamic compromise) while simultaneously minimizing the drawbacks (slow recovery time, increased post sedation emesis, and increased emergence reaction), recent research has examined the combination of lower-dose ketamine co-administered with propofol. An extensive literature search revealed that no prospective, randomized, controlled studies of ketamine/propofol have been reported. Only 2 prospective, observational studies were found in the recent literature relevant to the practice of pediatric emergency medicine. Several studies, however, including a recent review article, examined the use of ketamine/propofol in both the adult and the pediatric literature in various settings (ie, cardiac catheterization laboratory results, MRI studies, auditory brainstem response studies, and during gastroscopy). Sharieff et al conducted a prospective, observational pilot study consisting of 20 patients in which ketamine/propofol was given (0.5 mg/kg IV of ketamine followed by 1 mg/kg IV of propofol) for isolated forearm fracture reduction in a pediatric ED. This ketamine/propofol combination resulted in a median time from administration to the time the patient was ready for discharge of 38 minutes, which is significantly faster than the median times reported in other studies: 80 minutes using 1 mg/kg IV of ketamine in the study by Roback et al and 78 minutes using 1 mg/kg IV of ketamine plus 5 mcg/kg IV of glycopyrrolate. Another notable observational finding in the ketamine/propofol study by Sharieff et al is that 15 patients experienced desaturations (< 93%), but all responded to repositioning. None required oxygen administration or assisted ventilation.

Andolfatto et al conducted a larger prospective, observational study enrolling 219 patients. The ketamine/propofol combination used in their study was 1:1 (1 mg/kg IV of ketamine and 1 mg/kg IV of propofol, combined in one syringe). Sixty-eight percent of the patients received less than 1 mg/kg of each drug (with a median dose of 0.8 mg/kg of ketamine/propofol). In this study population, however, up to 20% of the patients received sedation for procedures that do not routinely require deep sedation (laceration repair, chest tube insertion, abscess incision and drainage, CT scan, foreign body removal, hernia reduction, lumbar puncture, cardioversion, laryngoscopy, and pelvic examination). The remaining 80% of patients required procedural sedation for orthopedic fractures (71%) or orthopedic dislocations (9%). The median total sedation time for this larger study was 18 minutes, which is significantly faster than those reported by Sharieff et al. The marked difference in total sedation time is most likely due to the lower doses of ketamine/propofol used in this study, the differences in definition of total sedation time between the 2 studies, and the variety of procedures in which ketamine/propofol was used for procedural sedation. Out of 219 patients, 7 (3.2%) had respiratory events associated with the sedation, which is similar to the incidence of respiratory events reported in other studies.

Both these observational studies strongly support the benefit that the ketamine/propofol combination seems to offer in terms of shorter length of sedation time but with no increase in adverse respiratory events, emesis, or emergence reactions. With ever-increasing ED volumes and the need to expedite patient flow into and out of ED beds, procedural sedation agents that have a shorter recovery time with minimal side effects are becoming more desirable. Further prospective, randomized, controlled studies comparing ketamine and ketamine/propofol need to be performed before one can conclude the combination regimen is faster than and as safe as ketamine alone. It should be noted that none of the above studies has examined the duration of subtle effects resulting from “subdissociative” doses of ketamine in terms of when a patient can be discharged.

Increased Intracranial And Intraocular Pressures

Ketamine has been routinely contraindicated in patients with significant head trauma or ocular trauma because early case reports and case series studies have shown that its use is associated with increases in intracranial and/or intraocular pressure. In the early 1970s, numerous studies (mostly case reports
to no effect on IOP, whereas sevoflurane caused a significant decrease in IOP. Although these recent studies seem to suggest that ketamine does not cause a clinically significant rise in IOP, the clinician could consider using another sedative or analgesic agent instead of ketamine in the setting of increased IOP or ocular trauma.

**Pharmacology**

The commercially available formulation of ketamine is a racemic mixture of 2 optical isomers, S(+) and R(-). Each isomer has been shown to have different properties, with the S(+) isomer having 2 to 3 times more potent analgesic properties than the R(-) isomer. Ketamine has been shown to interact with N-methyl-D-aspartate (NMDA) receptors, opioid receptors, and monoaminergic and muscarinic receptors. Although ketamine’s interactions with other receptors are still being elucidated, its non-competitive antagonism with NMDA receptors is well established. The NMDA receptor (a member of the glutamate receptor family) has been implicated in the mechanism underlying general anesthesia and analgesia. Ketamine’s potent analgesic properties are a result of complex interactions with the mu (μ), delta (δ), and kappa (κ) opioid receptors.

Ketamine has been described and categorized as a dissociative sedative agent. Through its interaction with the NMDA receptors, it effectively disconnects the thalamoneocortical system from the limbic system. This results in a “dissociated” state in which the patient does not respond to external stimuli. The trancelike dissociative state, also described in the literature as “cataleptic” state, lasts 5 to 10 minutes, with a slow return to baseline mental status over a period of approximately 1 hour.

After IV administration of 1 to 2 mg/kg of ketamine, it usually takes less than 1 minute for the patient to enter the state, at which point the eyelids open and nystagmus ensues, with the eyes in a fixed and centered gaze. The patient may exhibit tearing and salivation, and there is a baseline increase in heart rate and blood pressure thought to be due to an increased sympathomimetic response to direct stimulation of central nervous system structures. While in this state, corneal and light reflexes remain intact. Varying degrees of skeletal musculature hypertonicity occur, accompanied by occasional gross muscle movements unrelated to the external stimuli.

Unlike other sedative agents, ketamine does not affect the patient’s ability to maintain normal spontaneous respirations throughout the duration of sedation. Also of note, ketamine does not exhibit the usual dose-response continuum. The patient enters this dissociative state once a sufficient dose of ketamine (usually 1 mg/kg) exceeds the necessary threshold, and additional doses of ketamine do not result in a deeper state of sedation. Studies have
shown that subdissociative doses of ketamine (< 1 mg/kg IV or < 2 mg/kg IM) provide substantial analgesic effects without the added risk of adverse respiratory events in postoperative, oncologic, and chronic pain settings.88

**Prehospital Care**

Because of its potent analgesic effects with minimal adverse respiratory effects, ketamine, given IV or IM, has been studied in the prehospital setting.69 Many of the existing studies are retrospective in design and reveal promising results about the safety and efficacy of ketamine use in this setting. One retrospective study from the United Kingdom reviewed records from the trauma base for the London Helicopter Emergency Medical Service (HEMS). The HEMS response team consisted of a physician and a paramedic. A total of 1030 trauma patients received ketamine with or without midazolam for analgesia, rapid-sequence intubation, or sedation for painful procedures. Ketamine was given to patients with burns, fracture reductions/immobilizations, pain from blunt force trauma, and penetrating injuries. On detailed chart review, these researchers found that 0.6% of the patients had documented desaturations following ketamine administration, and 20.3% of the patients underwent rapid-sequence intubation following ketamine administration. The authors claim that none of these intubations was a result of airway compromise due to ketamine administration but instead were performed as part of the overall management plan for the patient.90

A second, smaller retrospective study conducted in the United States reviewed ketamine use in a regional aeromedical critical care transport program. The response team consisted of a flight physician and a nurse. A total of 40 patients were analyzed over a 3-year period. In this study, ketamine was given for both medical indications (status asthmaticus, hypotensive cardiac patients, burns, and combative patients) and trauma-related indications (pelvic/long bone fractures and pain control for extrication). All the patients maintained normal airway respon-

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**Risk Management Pitfalls In Pediatric Procedural Sedation**

1. “I must give an anticholinergic in conjunction with ketamine to minimize complications due to aspiration from salivary secretions.”
   Although atropine has been shown to decrease the amount of observed secretions, in numerous randomized, controlled studies, it has not been shown to be of any additional benefit in preventing airway complications.62-64

2. “I can’t give narcotics for pain relief prior to sedation because this could lead to complications with oversedation.”
   One retrospective chart review aimed at answering this question showed no significant differences in adverse events between patients who had received narcotics prior to sedation versus those who had not.59 Providing appropriate, preferably short-acting, analgesia while awaiting procedural sedation is the humane thing to do.

3. “This patient has multiple face and scalp hematomas from being an unrestrained passenger in a rollover motor vehicle collision. He needs sedation for fracture reduction prior to getting admitted. Can I use ketamine to sedate him?”
   Although the data are conflicting regarding the use of ketamine in patients with head injury/increased ICP, some studies have clearly documented increased ICP with ketamine adminis-

4. “I have a 3-month-old patient who needs sedation for femur fracture reduction and cast placement. Is ketamine a reasonable choice?”
   Children younger than 3 months of age seem to have more adverse respiratory events when treated with ketamine sedation.11,35 Therefore, it is probably better to use another agent, followed by prolonged post sedation monitoring or admission for overnight observation to ensure that no delayed adverse events occur.

5. “This patient has hypoesthesias and weakness in his hand from a forearm fracture. His last PO intake was 2 hours ago. I should therefore wait 2 more hours before I can sedate him, despite his neurologic deficits.”
   Several published guidelines recommend 4 to 6 hours of fasting before moderate or deep sedation, but this patient has a neurologic deficit that must be attended to promptly. Studies have shown that there is no relation between adverse respiratory events and fasting.93,94 In this patient, prompt reduction supersedes the risk of aspiration, and the procedure should be performed immediately. The clinician should always be
siveness and oxygen saturation levels.\textsuperscript{91} One caveat in both these studies is that the emergency response teams who administered the ketamine consisted of a physician and a nurse, which brings into question its safety and applicability in EMS systems when the response team consists solely of paramedics.

**Emergency Department Evaluation**

Emergency clinicians should familiarize themselves with the well-established and well-researched guidelines set forth by the AAP, ACEP, and the American Society of Anesthesiologists.\textsuperscript{8,10,92} Before performing procedural sedation, clinicians should question all prospective patients about preexisting medical conditions, any known allergies, any current medications (both prescription and herbal medications, as well as any recreational or illicit drug use), and prior complications with sedation in both patients and family members. This information can help alert the clinician to any potential risk factors for complications related with the use of ketamine. A detailed medical history should focus on eliciting any known factor that would contraindicate ketamine use in the patient. (See Indications And Contraindications on page 4.)

Clinicians should inquire about the time of the patient’s last intake of food or fluids. Current AAP guidelines suggest that the patient’s oral intake be restricted (NPO) for 2 hours for clear liquids, 4 to 6 hours for breast milk/formula, and 6 hours for light meals. These fasting times are often not feasible in a busy ED setting. Two recent studies have shown no difference in the incidence of adverse respiratory events or emesis in relation to the fasting times, which calls into question the need to adhere to these strict fasting guidelines in emergent situations.\textsuperscript{93,94} ACEP’s clinical policy on procedural sedation and analgesia in the ED states, “Recent food intake is not a contraindication for administering procedural sedation and anesthesia but should be considered in choosing the timing and target level of sedation.”\textsuperscript{9}

A focused physical examination should be performed, with particular attention paid to the mouth ready with appropriate suctioning and equipment to secure the airway in the event of emesis.

6. “This patient, whom I sedated with ketamine for a lumbar puncture to evaluate her headache and fever, has an elevated opening pressure. Does she have pseudotumor cerebri?”

The elevated opening pressure is most likely due to the ketamine. Several studies have shown that ketamine can increase ICP.\textsuperscript{17} If an opening pressure is needed to rule in or rule out a specific diagnosis, the clinician should choose a sedative agent other than ketamine to assure an accurate and valid opening pressure.

7. “Laryngospasm is so rare; I don’t need to have the emergency airway cart nearby during this sedation.”

Although laryngospasm is indeed rare, the clinician should be ready to respond immediately if and when it does occur. This includes having the appropriate equipment at or near the bedside. (Remember the SOAPME mnemonic: Suction, Oxygen, Airway equipment, Pharmacy medications, Monitors, and Equipment).\textsuperscript{8}

8. “The patient is getting ketamine, which is a potent analgesic, so he doesn’t need a digital block for repair of this fingertip amputation.”

Ketamine is a potent analgesic, but it is not uncommon for patients to flinch or move in response to painful stimuli. This is particularly true after the drug has reached its peak concentration and the dissociative anesthetic state starts to wane. The local infiltration of lidocaine or bupivacaine to the site will prevent discomfort but also movement during the procedure as he begins to wake up.

9. “Ketamine is unsafe to use in areas outside of the operating room.”

Several studies have explored the safety of ketamine use in EDs, sedation suites, and dental or ophthalmology clinics. The results indicate ketamine is safe in such settings as long as the appropriate guidelines are followed, monitoring and safety equipment are available, and the practitioner is well trained in recognizing and managing respiratory emergencies.

10. “I’ve given this toddler 1.5 mg/kg of ketamine, but the medication has lasted only a few minutes — not long enough to complete the procedure.”

According to several reports, higher ketamine doses are required for smaller children because children in general have a relatively larger volume of distribution than adults. It is not uncommon for smaller children to require higher doses or repetitive dosing to maintain the dissociative state.
and oropharynx to detect anatomic abnormalities that could result in airway compromise during sedation and to determine whether it might be difficult to secure the airway in an emergency. The evaluating clinician should perform a thorough cardiopulmonary examination to ensure normal ventilatory and cardiac function. Complete vital signs should be obtained, including baseline respiratory rate, heart rate, blood pressure, and oxygen saturation, as well as a recent weight, and these values should be documented in the nursing chart to ensure appropriate dosing of medications. Continuous end-tidal carbon dioxide monitoring (capnography) can be used as an adjunct for monitoring the patient during sedation and can be helpful in detecting laryngospasm, upper airway obstruction, or apnea before desaturations are noted.

**Special Circumstances**

Although ketamine is an excellent choice for providing both analgesia and deep sedation when given in appropriately therapeutic doses (1–2 mg/kg), it is not uncommon for patients to continue to react or respond to sharp, painful stimuli such as needlesticks or surgical incisions. By definition, deep sedation is when a patient cannot be easily roused but responds purposefully to repeated verbal or painful stimulation. To help prevent further patient movement during the procedure, as well as to provide postprocedural analgesia, the infiltration of a local anesthetic such as lidocaine (or buffered lidocaine) or bupivacaine is recommended in areas where the procedure might inflict sharp pain. Examples include lidocaine infiltration in the perilumbar skin area for lumbar punctures or lidocaine with epinephrine at the incision site for abscess incision and drainage. The addition of a local anesthetic will further minimize pain and may reduce the total amount of ketamine required during key stages of delicate procedures.

**Laryngospasm**

Laryngospasm is the spasmodic closure of the glottic aperture. It usually occurs shortly after the administration of ketamine and is manifested by lack of chest wall excursion, a sudden drop of EtCO₂ measurements to 0 with an associated flat line on continuous capnography, a decrease in oxygen saturation, and associated signs of upper airway obstruction. Although relatively infrequent (0.4% incidence noted in one study), laryngospasm can be a dangerous and potentially life-threatening complication of ketamine administration, and the clinician should be prepared to treat this complication if it should arise.

According to the AAP guidelines, a minimum of 2 persons should be present at the patient’s bedside during moderate or deep sedation. One person, usually a nurse, is responsible for recording and monitoring physiologic parameters (e.g., respiratory rate, blood pressure, and oxygen saturations, with or without capnography) and assisting the practitioner in the event of an emergency. The other person (the clinician who is performing the sedation) should:

- Be responsible for treating the patient, administering the medication, and providing any necessary interventions in the event of complications from the sedation
- Be familiar with the medications given and any associated side effects
- Be able to recognize and correct any potential adverse effects that occur as a result of the sedation
- Be well-trained and competent in advanced airway management, including effective bag-valve-mask ventilation and, if necessary, intubation to secure a definitive airway

When laryngospasm occurs, the classic teaching is to perform a jaw-thrust maneuver, followed by gentle but constant positive-pressure ventilation with 100% oxygen using a bag and mask of appropriate size. If this fails to resolve the laryngospasm, the practitioner should administer a paralytic drug (e.g., succinylcholine) to relax the vocal cord musculature and should subsequently ventilate the patient with a bag-valve-mask or consider intubation until the paralytic has worn off. For the prompt management of acute laryngospasm, there is also mention of a “laryngospasm notch” in the anesthesiology literature; however, there was nothing in the literature that elucidated the neuroanatomic mechanism by which this maneuver works. This notch is located bilaterally in the depression beneath the earlobes; it is bounded by the mastoid process posteriorly, the superior portion of the rami of the mandible anteriorly, and by the base of the skull superiorly. The practitioner performs the maneuver by applying firm, constant pressure with the middle fingers in the area of the notch, medially and toward the base of the skull, while simultaneously lifting the mandible anteriorly much like the jaw-thrust maneuver. With this maneuver, the laryngospasm should resolve within 1 to 2 breaths, but if not, the practitioner should continue to apply such pressure, which is usually successful within 4 to 5 breaths.

The potential for laryngospasm to occur provides the rationale for ensuring 100% oxygenation prior to and during a procedure to allow sufficient time to treat this problem should it arise.

**Emergence Reactions And Psychiatric Events**

The incidence of ketamine-associated emergence reactions is difficult to ascertain, given the lack of a standard definition of what this reaction constitutes.
In their review article, Strayer and Nelson found that psychiatric events occurred in 10% to 20% of patients receiving ketamine. As mentioned earlier, the co-administration of ketamine and benzodiazepines (most notably midazolam) does not reduce the occurrence of emergence reactions. In the event that a patient wakes up with severe agitation or hallucinations following ketamine administration, as-needed doses of benzodiazepines have been shown to be effective in treating this agitated state.

**Nausea And Emesis**

The incidence of ketamine-associated nausea and emesis ranges from 3.8% to 18.7%. As mentioned earlier, one randomized, controlled trial showed that the co-administration of ondansetron and ketamine at the start of the procedure significantly reduced the incidence of ketamine-related nausea.

**Controversies/Cutting Edge**

**Ketamine For Treatment Of Refractory Status Epilepticus**

According to recent anecdotal and experimental studies, ketamine can be used to treat patients with refractory status epilepticus. Current animal models of the propagation and maintenance of status epilepticus suggest that inhibitory \(-\)aminobutyric acid (GABA) receptors on the neuronal surface are increasingly internalized/downregulated the longer the seizure persists. Simultaneously, neuroexcitatory NMDA receptors are moved to the synapse. Current therapies, such as benzodiazepines and barbiturates, which exert their inhibitory effect on neuronal activity through GABA receptors, may not be effective in the case of refractory status epilepticus because of the internalization of these receptors. Ketamine, being an NMDA antagonist, potentiates the neuroexcitatory propagation seen in status epilepticus by interacting with upregulated NMDA receptors at neuronal synapses. Because of its competitive antagonism of NMDA receptors, ketamine has been shown, both anecdotally and experimentally, to stop refractory status epilepticus. Further research to clarify the exact timing and dosing of ketamine needs to be conducted.

**Ketamine And Apoptosis Or Neuronal Cell Death**

Over the past decade, an increasing amount of evidence has emerged linking ketamine and other NMDA-receptor antagonists to apoptosis and neuronal degeneration in the brains of young animal models (rats, mice, and nonhuman primates). The administration of NMDA antagonists, such as ketamine, during this critical period of brain development (during synaptogenesis) resulted in a robust apoptotic neurodegenerative response. Synaptogenesis is estimated to extend from the third trimester of pregnancy to the first several years of life in humans, during which time the developing brain is extremely sensitive to both overstimulation (via NMDA-receptor stimulation), resulting in excitotoxic neurodegeneration, and understimulation (via GABA-receptor inhibition), resulting in apoptotic neurodegeneration.

The implied public health concern is that some of the anesthetic and sedative agents that are commonly used in infants and children could have deleterious effects on the developing brain. Learning disabilities, hyperactivity, and attention deficit disorder as well as adult-onset depression or psychosis are some of the possible consequences of neurodegeneration and apoptosis during synaptogenesis. As a result of this emerging literature, the Food and Drug Administration held a meeting in March of 2007 to discuss the public health implications of using ketamine and other anesthetic agents in the pediatric population. The committee concluded that the results of these animal studies, while worrisome, could not reliably be extrapolated to humans. Of note, the existing animal studies used significantly higher doses (20–50 mg/kg) or used ketamine for prolonged or excessively repetitive doses that are not commonly used in the ED setting, calling into question its effect when translated to humans.

**Ketamine Isomers**

The currently available formulation of ketamine (Ketalar®) consists of a racemic mixture of the drug’s R(-) and S(+) isomers. In the past decade, more animal and human research has focused on separating, isolating, and subsequently studying the properties of the R(-) and S(+) isomers of ketamine with hopes of improving ketamine’s sedative and analgesic properties and minimizing its unwanted side effects. A majority of the more recent studies have focused on the S(+) isomer, which has shown a lot of promise as a potent analgesic in preliminary studies. One study suggested that less S(+) ketamine was needed to attain the same sedative/analgesic effects in pediatric patients who required sedation for cardiac catherization. Future research on the benefits and drawbacks of these isomers will need to be carried out to refine our understanding of ketamine’s isomers and their potential use in the ED setting.

**Disposition**

Following the completion of the procedure, patients who have undergone ketamine procedural sedation should be monitored closely for the development of any adverse respiratory or behavioral events. Newman et al conducted a prospective observational study looking for the adverse effects following procedural sedation and found that a majority
of these occurred within 30 minutes of the drug administration.\textsuperscript{107} Given the relatively short duration of ketamine and the lack of reports of any delayed adverse respiratory events occurring, most patients can be observed closely in a monitored setting until return to baseline mental status as recommended by the AAP guidelines\textsuperscript{8,11} and the ketamine clinical practice guideline recommended by Green et al.\textsuperscript{8,11} Parents should be warned about the potential occurrence of emesis as well as rare but possible behavioral changes and nightmares that may occur after hospital discharge.\textsuperscript{59}

### Summary

ED clinicians who take care of pediatric patients strive to provide the most compassionate yet safe care for our patients. The classic story of the toddler who presents with a forearm fracture from a fall is not only in significant pain but is also frightened and will most likely be uncooperative during the evaluation and management of his or her injury. With a better understanding of the risks and benefits of procedural sedation and analgesia, we can provide effective and safe care to these patients in the ED. In the search to find the perfect agent that will provide rapid and sufficient sedation and analgesia for a majority of the painful procedures, ketamine has quickly become one of the more frequently used medications for procedural sedation and analgesia in the ED. Some of the many reasons for ketamine’s popularity are its ability to provide sedation and analgesia of rapid onset (with a reasonably wide therapeutic window) dosing via multiple routes of administration, and a brief duration of sedation along with a low incidence of manageable side effects. Over the past 40 years, numerous studies have revealed the benefits and drawbacks of ketamine. Although more studies continue to be conducted to refine the use of this agent and improve its safety, particularly in the young, developing brain, ketamine has managed to withstand such rigorous scrutiny and has become a cornerstone in the armamentarium for pediatric procedural sedation and analgesia in the ED setting.

### Case Conclusions

While waiting for the orthopedic team to set up and prepare for presurgical sedation, you give Patient 1, the 6-year-old boy with a radius and ulnar fracture, 1 mcg/kg of fentanyl IV for analgesia. This markedly alleviates his discomfort, to his parents’ great relief. After taking note of his fasting status and his history of mild asthma, you decide that he is a safe candidate for sedation with ketamine. Appropriate sedation levels are achieved with 1 mg/kg of ketamine IV. The orthopedic surgeon reduces the fracture without complications, and the patient is then monitored closely without incident.

After completing the sedation procedure for treatment of the forearm fracture, you move on to Patient 2, the 2-year-old-girl. Her complex lip laceration will require plastic surgery. You thoroughly examine her head, pupils, tympanic membranes, and scalp and find no clinical evidence of intracranial injury. Although you realize that her recent PO intake makes sedation less than ideal, you decide to proceed by giving her 0.15 mg/kg of ondansetron IV to prevent ketamine-associated emesis. You premedicate with atropine, 0.02 mg/kg IV, several minutes prior to the ketamine dose to minimize the amount of salivary secretions, thereby lowering the risk of aspiration while simultaneously allowing the plastic surgeon to work in a drier field. You then administer ketamine, 1 mg/kg IV, and achieve the appropriate level of sedation. The plastic surgeon infiltrates local anesthetic to the lip and completes the laceration repair without incident. Toward the end of the procedure, the patient starts to wake up. She is then monitored, emesis having been prevented, and is discharged home with outpatient follow-up.

### References

Evidence-based medicine requires a critical appraisal of the literature based upon study methodology and number of subjects. Not all references are equally robust. The findings of a large, prospective, randomized, and blinded trial should carry more weight than a case report.

To help the reader judge the strength of each reference, pertinent information about the study, such as the type of study and the number of patients in the study, will be included in bold type following the reference, where available. In addition, the most informative references cited in this paper, as determined by the authors, will be noted by an asterisk (*) next to the number of the reference.


40. Misra S, Mahajan PV, Chen X, et al. Safety of procedural...


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1. Which of the following is NOT one of the side effects associated with ketamine:
   a. Hypertension
   b. Abdominal pain
   c. Nystagmus
   d. Increased salivary secretions

2. The reversal agent for ketamine is:
   a. Flumazenil
   b. Naloxone
   c. Benadryl
   d. There is no reversal agent for ketamine

3. Which of these is true of IV ketamine versus IV fentanyl/Versed®?
   a. IV ketamine requires a longer recovery than IV fentanyl/Versed®
   b. IV ketamine causes more adverse respiratory events (desaturations) than IV fentanyl/Versed®
   c. IV ketamine causes less emesis than IV fentanyl/Versed®
   d. Parents were more satisfied with IV fentanyl/Versed® than they were with ketamine

4. Which of the following procedures would ketamine be a POOR choice to use for sedation:
   a. Lumbar puncture
   b. Fracture reduction
   c. Abscess incision and drainage
   d. MRI scanning

5. Which agent when administered in conjunction with ketamine helps decrease the incidence of post sedation emesis?
   a. Glycopyrrolate
   b. Ondansetron
   c. Promethazine
   d. Morphine

6. Which of the below is an absolute contraindication for ketamine use:
   a. Last PO liquids 4 hours earlier
   b. Age < 18 months
   c. Acute psychosis
   d. History of vomiting after ketamine administration

7. One minute into the ketamine sedation of a 6-year-old patient you notice that his chest wall stops moving and his oxygen saturation starts to drop. According to the monitor, both blood pressure and heart rate are slightly elevated compared with baseline levels. What is causing his acute decompensation?
   a. Monitor malfunction
   b. Rigid chest syndrome
   c. Laryngospasm
   d. Anaphylaxis

8. Your immediate response to assist the patient in Question 6 should be to:
   a. Perform a jaw-thrust maneuver and begin positive-pressure ventilation with bag-valve-mask.
   b. Check the pulse oximeter on another extremity.
   c. Administer naloxone.
   d. Give IM epinephrine.
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Goals & Objectives: Upon reading Pediatric Emergency Medicine Practice, you should be able to: (1) demonstrate medical decision-making based on the strongest clinical evidence; (2) cost-effectively diagnose and treat the most critical ED presentations; and (3) describe the most common medical pitfalls for each topic covered.

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Coming In Future Issues

Assessment and Management Of Acute Bronchiolitis In The Emergency Department

This issue of Pediatric Emergency Medicine Practice will focus on the challenges of effective evaluation and treatment of pediatric patients with bronchiolitis using evidence-based medicine. While excellent published guidelines do exist to help clinicians to address this common disease, they exclude the “high risk” group for severe bronchiolitis who are at risk for serious complications such as apnea and the need for ventilatory support. Particularly helpful in this area is the American Academy of Pediatrics (AAP) Subcommittee on Diagnosis and Management of Bronchiolitis. Novel treatment for acute bronchiolitis such as nebulized hypertonic saline, heliox, and the use for nasal continuous positive airway pressure will be discussed in this article.

In This Month’s Emergency Medicine Practice

An Evidence-Based Approach To Managing The Anticoagulated Patient In The Emergency Department by Dennis Hanlon, MD, FAAEM, Vice Chairman of Emergency Medicine; Associate Professor of Emergency Medicine, Drexel University College of Medicine, Allegheny General Hospital, Pittsburgh, PA

You start another busy shift with a double row of charts waiting to be seen. Your first patient is an elderly man who fell an hour prior to presentation. He did not lose consciousness, but was dizzy for a few minutes. He complains of a mild headache but denies any neck pain. He takes warfarin for valvular heart disease. He looks good and has no focal neurological complaints. His mental status is normal, he has a negative head CT scan, and his INR is 3.9 His family wants to take him home, which would help relieve some of the congestion in the ED, but you wonder what would be best. To observe and repeat imaging? Reverse his anticoagulation? Change his dosing regimen of warfarin?

In the next room, you quickly evaluate a 51-year-old obese woman with nonspecific back and abdominal pain that started 24 hours before and has slowly progressed to become intolerable. She denies fever, chills, nausea, or vomiting. She is on the last day of a 5-day course of ciprofloxacin for a UTI. She takes warfarin for a pulmonary embolus that occurred 2 months prior. Her hematocrit is mildly decreased, and her white blood count is normal; however, the INR is 6.8. You wonder if her abdominal pain is related to the UTI or if it could be somehow related to the prolonged INR. In fact, you wonder why her INR is so prolonged. . . .

This issue of Emergency Medicine Practice focuses on the challenge of evaluating and managing the anticoagulated patient using the best available evidence from the literature. The main complication of this therapy is hemorrhage which can be life-threatening, depending on its location. This issue also addresses the patient taking antiarrhythmic or antiplatelet agents and includes discussions of prothrombin complex concentrates and the off-label use of recombinant Factor VII (rFVIIa).

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Patient Satisfaction
In The Pediatric Emergency Department

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