Original Article

Adverse Events Associated With Procedural Sedation in Pediatric Patients in the Emergency Department

Magdalena E. Cudny, PharmD, BCPS^{*}; N. Ewen Wang, MD[†]; Sandra L. Bardas, BSP, FCSHP[‡]; and Carolyn N. Nguyen, PharmD[‡]

Abstract

Purpose: To determine the agents used by emergency medicine (EM) physicians in pediatric procedural sedation and the associated adverse events (AEs) and to provide recommendations for optimizing drug therapy in pediatric patients.

Methods: We conducted a prospective study at Stanford Hospital's pediatric emergency department (ED) from April 2007 to April 2008 to determine the medications most frequently used in pediatric procedural sedation as well as their effectiveness and AEs. Patients, 18 years old or younger, who required procedural sedation in the pediatric ED were eligible for the study. The data collected included medical record number, sex, age, height, weight, procedure type and length, physician, and agents used. For each agent, the dose, route, time from administration to onset of sedation, duration of sedation, AEs, and sedation score were recorded. Use of supplemental oxygen and interventions during procedural sedation were also recorded.

Results: We found that in a convenience sample of 196 children (202 procedures) receiving procedural sedation in a university-based ED, 8 different medications were used (ketamine, etomidate, fentanyl, hydromorphone, methohexital, midazolam, pentobarbital, and thiopental). Ketamine was the most frequently used medication (88%), regardless of the procedure. Only twice in the study was the medication that was initially used for procedural sedation changed completely. Fracture reduction was the most frequently performed procedure (41%), followed by laceration/suture repair (32%). There were no serious AEs reported.

Conclusion: EM-trained physicians can safely perform pediatric procedural sedation in the ED. In the pediatric ED, the most common procedure requiring conscious sedation is fracture reduction, with ketamine as the preferred agent.

Key Words—adverse events, emergency department, ketamine, pediatric patients, procedural sedation

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Painful and frightening procedures are frequently necessary during emergency care of children. To relieve the pain and alleviate anxiety associated with a painful procedure as well as to facilitate a controlled accomplishment of diagnostic and therapeutic procedures, procedural sedation is often used in the emergency department (ED). Procedural sedation is accompanied by the administration of consciousness-

altering medications, and these medications are not without risks. Historically, anesthesiologists trained in the administration of these potentially dangerous medications played a key role; however, as the number of children in the ED increases, emergency medicine (EM) physicians with different degrees of comfort and training are now providing pediatric procedural sedation and administering

^{*}Clinical Pharmacist, Department of Pharmacy, Stanford Hospital and Clinics, Stanford, California; [†]Associate Professor, Department of Surgery, Division of Emergency Medicine, Stanford University School of Medicine, and Associate Director of Pediatric Emergency Medicine, Stanford Hospital and Clinics, Stanford, California; [‡]Clinical Pharmacist, Emergency Medicine, Stanford Hospital and Clinics, Stanford, California. Corresponding author: Magdalena E. Cudny, PharmD, BCPS, Department of Pharmacy, Stanford Hospital and Clinics, 300 Pasteur Drive, Stanford, CA 94305; phone: 650-725-5299; fax: 650-736-8781; e-mail: mcudny@stanfordmed.org

agents that were previously in the realm of the anesthesiologist.¹⁻⁵

The administration of procedural sedation agents by EM physicians remains a cornerstone of national safety initiatives.⁶ Non-anesthesiology-trained practitioners must be well trained in the administration of these agents to maintain safety standards set forth for anesthesiologists. Other members of a multidisciplinary team must also be well versed in the administration of these agents. Pharmacy services in the ED are expanding, and pharmacists can play a key role in the safe provision of pediatric conscious sedation.

Limited literature is available regarding the current practice and safety outcomes of procedural sedation by EM-trained physicians in university-based pediatric EDs.⁷ Questions remain as to what agents and doses are appropriate for successful and safe pediatric sedation. The literature that does exist examines single agents and does not include comparisons between 2 or more agents.^{8,9} Published peer-reviewed literature strongly supports the EM physician's ability to safely and effectively administer procedural sedation in the ED; however, there is no clear guidance on how to best execute this practice.

We undertook this study to determine the types of agents used by EM physicians in pediatric procedural sedation and their associated adverse events (AEs) and to provide recommendations for optimizing drug therapy in these patients.

METHOD

Stanford Hospital and Clinics is an acute and tertiary care teaching hospital with a 32-bed adult and pediatric Level 1 ED. The pediatric ED houses 9 pediatric beds and is staffed by an attending physician and pediatric and EM residents. Pharmacy services include a satellite pharmacy staffed daily with 1 full-time clinical pharmacist from 2:00 p.m. to midnight. Pharmacy services provided to the ED are consistent with recommendations of the American Society of Health-System Pharmacists.¹⁰ The clinical pharmacist in the ED reviews and verifies orders using a computerized prescriber order entry (CPOE) system, obtains medication from a controlled-access cabinet, and draws-up and dispenses the medication.

We conducted a prospective study at Stanford Hospital and Clinics pediatric ED from April 24, 2007 to April 7, 2008 to determine the medications most frequently used in pediatric procedural sedation as well as their effectiveness and AEs. Pediatric patients, 18 years old or younger, who required procedural sedation in the pediatric ED during the hours of 2:00 p.m. to midnight were eligible for the study. Consent

from the patient or guardian (if younger than 18 years of age) was obtained for all participants. The consent form is a standard form issued by Stanford Hospital and Clinics to all patients undergoing minimal to moderate procedural sedation in the ED. The protocol was approved by the Stanford Hospital and Clinics' Institution Review Board (IRB) on April 5, 2007.

The data were collected by pharmacy residents, clinical pharmacists, and nurses (when the pharmacist could not be present for the whole procedure) and recorded on an IRB approved data collection sheet (Appendix A). The data were transcribed into a password-protected *Microsoft Excel* (Microsoft Corp, Redmond, WA) spreadsheet and stored on a flash drive in a locked pharmacy cabinet. Variables collected included patient name, medical record number, sex, age, height, weight, type of procedure, length of procedure, physician, and agents used. For each agent that was used, dose (mg/kg), route, time from administration to onset of sedation, duration of sedation, AEs, and sedation score were recorded. Use of supplemental oxygen and interventions during procedural sedation were also recorded.

With the exception of physician name, agent used, and route, all data entry was through free text. Medications were recorded using drop-down boxes with the following prespecified agents: ketamine, etomidate, fentanyl, hydromorphone, methohexital, midazolam, and pentobarbital. If the agent used was not listed in the drop-down menu, it was specified in the comments section. If multiple doses of the same agent were used during a given procedure, that agent was counted once and the total dose was recorded.

The level of sedation was based on the Ramsay Sedation Scale (RSS), which scores sedation at 6 levels. The RSS defines the sedation state from level 1 (the patient is anxious, agitated or restless) through the continuum of sedation to a level 6 (the patient is completely unresponsive) (Table 1).¹¹ An RSS score of 5 to 6 was defined as effective sedation for this study.

AEs during procedural sedation were recorded for each agent and grouped into categories by body system. There were no pre-established standardized terms for sedation-related AEs. Minor and serious AEs were recorded. A serious AE was defined as an event that was associated with an invasive, corrective intervention such as intubation, bag mask application, placement of an artificial airway, or hospitalization directly related to the procedural sedation. Face masks and nasal cannula were usually placed prior to the procedure as pre-emptive measures and not as a result of an AE related

to the medication. A single patient may have had more than 1 AE or intervention.

Descriptive statistics, compiled with *Microsoft Excel*, were used to analyze the data. The percentage of procedures performed and agents used in these procedures were calculated.

RESULTS

Data were collected for 202 procedural sedation cases involving 196 pediatric patients (Table 2). Patients' ages ranged from 8 months to 18 years (median, 5 years).

Procedures were classified by length of procedure, need for supplemental analgesia in addition to sedation, and need for immobility. Procedures performed included fracture reduction (84; 41%), laceration/suture (64; 32%), incision and drainage (I&D)/arthrocentesis/aspiration (25; 12%), lumbar puncture (10; 5%), sedation for radiology (6; 3%), foreign body removal (5; 3%), and other (8; 4%) (Figure 1).

Agents Used

Medications used in procedural sedation included ketamine, etomidate, fentanyl, hydromorphone, methohexital, midazolam, pentobarbital, and thiopental. In 178/202 (88%) procedures, only 1 agent was used by the ED physician. Ketamine as the only agent was used in 144/178 (81%) of these procedures, followed by methohexital (25), midazolam (4), etomidate (3), pentobarbital (1), and thiopental (1). Fentanyl and hydromorphone were not used as the sole agents in any of the procedures. The average onset and duration of action of ketamine intravenous (IV) was 30 seconds and 15 minutes, respectively. The most frequently used dose of ketamine IV was 1 mg/kg (36%) with duration of action of 10 minutes. However, 52% of the patients needed a repeat dose. A single unrepeated dose of ketamine IV 1.5 mg/kg was the most effective dose. The single unrepeated and most effective dose of ketamine intramuscular (IM) was 4 mg/kg (16%). The

onset of 5 to 10 minutes and duration of action of 5 to 90 minutes were observed with ketamine IM.

As a single agent, thiopental per rectum 25 mg/kg was used in 1 patient during sedation for a radiology procedure. The patient was sedated 58 minutes for a 4-minute procedure with an RSS score of 3.

Two agents were used in 24/202 cases (12%). Fentanyl and midazolam were used in combination in 7 procedures. The median RSS score was 2 in procedures that used fentanyl and midazolam together as the agents. The doses ranged from fentanyl IV 0.73 to 5 mcg/kg and midazolam IV 0.03 to 0.15 mg/kg. One patient received methohexital IV 1 mg/kg in addition to midazolam and fentanyl. In 2 cases, a true medication switch occurred. In 1 case, in addition to fentanyl and midazolam, the patient required methohexital for splinting during fracture reduction of the wrist. In another fracture reduction case, the patient experienced burning at the injection site during administration of methohexital IV and the medication was switched to ketamine IM. In the other cases, the different medications used in a single procedure were not considered a true medication switch and did not result from an AE. The median RSS score after the first agent was 3 and the second agent was 5.

Preferred Medications by Procedure Performed

Fracture reduction was the most common procedure performed in the pediatric ED (84/202; 41%). In majority of the fracture reduction cases (73/84; 87%), only 1 medication was used by the ED physician. The most common single agent used in this procedure was ketamine (53/84; 63%). Methohexital was the second preferred agent (17/84; 20%). Etomidate as a single agent was used in 2/84 (2%) of the cases, and midazolam was used in 1/84 (1%) case.

Ketamine was dosed IV in 46 cases and IM in 7 cases. The median doses of IV and IM ketamine in fracture reduction procedures were 1 mg/kg and 3.5 mg/kg, respectively. The median RSS for ketamine IV and IM dosing was 6. In 1 case, IM ketamine was switched to IV ketamine during the reduction procedure. This patient received ketamine IM 2 mg/kg with an RSS of 1. The patient woke up and cried out in pain, after which an IV was placed and ketamine 1 mg/kg IV was administered. The RSS score after the ketamine IV administration was 6.

There were 11 fracture reduction procedures in which more than 1 agent was used. One patient required 3 agents during the fracture reduction procedure. The agents, all IV, were fentanyl 1.6 mcg/kg, midazolam 0.8 mg/kg, and methohexital 1 mg/kg.

Table 1. Ramsay Sedation Scale for pain assessment

1 = Anxious and agitated or restless or both
2 = Cooperative, orientated, and tranquil
3 = Responds to commands only
4 = Brisk response to a light glabellar tap/loud auditory stimulus
5 = Sluggish response to a light glabellar tap/loud auditory stimulus
6 = No response to a light glabellar tap/loud auditory stimulus

Table 2. Patient demographics and clinical characteristics (N = 196)

Subjects	n (%) ^a
Age ^b	
0-1 year (<2 years)	27 (14)
2-10 years	133 (68)
11-18 years	36 (18)
Median (range)	5 years (8 months to 18 years)
Sex	
Female	82 (42)
Male	114 (58)
Procedures	(n = 202) ^{c*}
Fracture reduction	84 (41)
Laceration/suture	64 (32)
Incision and drainage/arthrocentesis/aspiration	25 (12)
Lumber puncture	10 (5)
Sedation for radiology	6 (3)
Foreign body removal	5 (3)
Other ^d	8 (4)

^aValues given as n (%) unless otherwise indicated.

^b0-12 months = infant; 2-10 years = toddler/child; 11-18 years = adolescent.

^cOne participant required 3 different procedures on the same encounter date and 2 of the participants required 2 different procedures on the same encounter date. Two participants required 2 different procedures on 2 different encounter dates. All these procedures were counted separately.

^dOther: ventricular tap (1), tooth extraction (1), chest tube placement (2), urinary catheterization (1), fecal disimpaction (1), wound debridement (1), and intravenous start (1).

Laceration/suture repair was the second most common procedure performed in the ED (64/202; 32%). Ketamine as a single agent was used in 90% (58/64) of these cases. The agents used in the remaining cases included midazolam and fentanyl or methohexital. The preferred doses of ketamine IV and IM were 1 mg/kg (24/58; 41%) and 4 mg/kg (17/58; 30%). However, 50% of the patients who received ketamine IV 1 mg/kg had to be re-dosed with additional ketamine IV.

Medication Reactions and Adverse Events

Various reactions to medications occurred in 71% (139/196) of the patients. These reactions are classified by body system and summarized in **Table B1**. Only respiratory reactions were viewed as true AEs.

Among the patients who experienced a medication reaction, supplemental oxygen such as a nasal cannula or face mask was used in 45% (63/139) and 19% (26/139), respectively. However, it is not clear whether supplemental oxygen was initiated as result of a complication or was a preemptive measure to avoid a complication. A total of 4 patients (3 fracture reductions, 1 laceration repair) required a jaw thrust.

One of the patients who required a jaw thrust also required a face mask for supplemental oxygen.

In 1 fracture reduction procedure, which lasted 8 minutes, ketamine IM 4 mg/kg was administered with a duration of sedation of 75 minutes. The jaw thrust was a result of excess salivation that also required suctioning. The second fracture reduction procedure lasted 73 minutes, with duration of sedation of 6 minutes due to fentanyl IV 1 mcg/kg and methohexital IV 1 mg/kg. This patient's jaw thrust was administered due to snoring as the patient's oxygen saturation remained normal. The third patient who required a jaw thrust during a fracture reduction procedure was sedated for 5 minutes during an 8-minute procedure. The patient who required a jaw thrust during a 17-minute suture procedure of a chin laceration received ketamine IM 3 mg/kg. The duration of sedation was 36 minutes, and there were no noted changes in the patient's oxygen saturation.

A total of 144/202 (71%) patients in the study received ketamine as the sole agent. The study revealed that 76% (109/144) of the patients who received ketamine had a medication reaction. The medication reactions noted with ketamine IV and IM regardless

Figure 1. The number and type of procedures requiring sedation in pediatric emergency department patients (N=196). Multiple procedures on a single patient were counted as a separate procedure for purposes of the medication selected or complication, although the individual patient was included only once in the total patient count. I&D = incision and drainage.

of the procedure were consistent with what is reported by the manufacturer in the package insert. There were 6 respiratory AEs observed (eg, apnea 4, tachypnea 1, and hypoxia 1) in patients who received ketamine.

Out of the 109 patients who received ketamine and experienced a medication reaction, 68 received ketamine IV and 39 received ketamine IM. Two patients received both ketamine IM and ketamine IV. In these patients, ketamine IM was initially administered and was followed by ketamine IV due to inadequate sedation before the medication reaction. There were 6 respiratory AEs reported in patients who received only ketamine. In the ketamine IV group, there were 3 cases of apnea and 1 of tachypnea. In the ketamine IM group, there was 1 case of apnea and 1 of hypoxia. Medication reactions due to ketamine IV and ketamine IM are broken down by body system and reported in Table 3.

Of the patients in the study who only received ketamine, 49/144 received ketamine IM and 91/144 received ketamine IV. Out of 91 patients who received ketamine IV, there was an average of 1.5 medication events per patient. Out of 49 patients who received ketamine IM, there was an average of 1.8 medication events per patient (Table B2). Four patients received both IV and IM ketamine and were not included in the count. There were no hospitalizations due to an AE reported in the study.

DISCUSSION

We found that in a convenience sample of 196 children (202 procedures) who were receiving procedural sedation in a university-based ED, 8 types of medications were used (ketamine, etomidate, fentanyl, hydromorphone, methohexital, midazolam, pentobarbital, and thiopental). Ketamine was the most frequently used medication (88%), regardless of the procedure. Only twice in the study was the initial medication used for procedural sedation changed completely. Fracture reduction was the most frequently performed procedure (41%), followed by laceration/suture repair (32%). There were no serious AEs reported.

The optimal dosing of ketamine appeared to be 1.5 mg/kg IV or 4 mg/kg IM, regardless of the procedure. The most common initial dose of ketamine IV was 1 mg/kg, with majority of the patients requiring a re-dose due to inadequate sedation. We presume that a longer procedure would require a second dose. If the ED practitioner can determine the length of the procedure on initial assessment, the ED clinical pharmacist can anticipate the need for a repeat dose and prepare the medication ahead of time.

Medication reactions were consistent with the profile of the medications, and no serious AEs were reported. The most common reactions reported with ketamine IV and IM were nystagmus, lacrimation, salivation, and vocalization. When other medications were chosen, notable effects included a prolonged period of sedation or inadequate sedation but no serious AEs were observed. Four episodes of jaw thrust occurred. Three of the jaw thrusts occurred during a fracture reduction procedure, and 1 occurred during a repair of a chin laceration. Two of the patients who required a jaw thrust received ketamine 3 mg/kg and 4 mg/kg IM and experienced long durations of sedation (36 and 75 minutes, respectively). The other 2 patients received repeated doses of fentanyl and methohexital IV during fracture reduction procedures. None of the patients experienced a drop in oxygen saturation. When multiple agents were used during a given procedure, it was difficult to identify which agent was responsible for a medication reaction without a wash-out period. This limitation mimics real-life scenarios where multiple agents are used in the ED to quickly execute a procedure and facilitate discharge. Furthermore, there was no predetermined list and/or standardized terms of possible sedation-related complications set prior to the study. This enabled us to capture all the AEs associated with an agent; however, this lack of standardization can increase misreporting.

Table 3. Medication reactions observed in pediatric emergency department patients after ketamine: intravenous vs intramuscular administration

Body system medication reactions	Intravenous ketamine (n=91) ^a	Intramuscular ketamine (n=49) ^a
Body as a whole		
Shivering	2	2
Cardiovascular		
Hypertension	2	0
Tachycardia	8	4
Digestive		
Salivation	14	15
Vomiting	1	8
Central nervous system		
Dizziness	3	1
Ataxia	1	0
Ocular		
Nystagmus	33	13
Lacrimation	20	10
Diplopia	4	0
Blurry vision	2	0
Neuromuscular and skeletal		
Skeletal muscle tone enhanced (tonic-clonic movements)	5	4
Restless leg syndrome	1	1
Facial tremor	1	0
Respiratory		
Apnea	3	1
Tachypnea	1	0
Hypoxia	0	1
Skin and appendages		
Injection site reactions	0	1
Facial flushing	0	1
Urogenital		
Urinary urgency	1	0
Urinary incontinence	1	1
Miscellaneous		
Vocalization	21	16
Hiccups	0	6
Yawning	0	1
Grimace	4	0
Agitation	3	0
Dysphoric emergence	4	1
Confusion	1	0
Protruding tongue	4	3

^aTwo patients were seen on 2 different encounters and the adverse events were counted separately.

Our experience supports the practice of EM physicians providing safe execution of pediatric procedural sedation in a university-based ED. Our study was not limited to certain procedures or agents used, so we were able to capture a wide variety of scenarios in which AEs can occur. Because there were no serious AEs reported, we feel that our procedural sedations were performed with successful outcomes and minimal morbidity. The benefits of delivering timely treatment in the ED combined with safe procedural sedation in collaboration with ED staff indicate that the performance of sedation in the ED is advantageous.

Limitations of this study include a lack of pre-defined categories and the use of free text to collect data. Data may have been cleaner if data collection was based on drop-down boxes with pre-specified selections in entry fields of the data collection sheet. Study data were collected by multiple individuals, which allowed for variable interpretation and entry of procedural results. During the analysis, categories such as procedures performed, agents used, and AEs reported had to be established to group the variable entry results and allow for thorough analysis of the data. However, the limited categories allowed us to capture in-depth data in a field where there are limited data reported in literature. We were able to capture an array of medications used in procedural sedation and determine the safety of administering these medications in a non-anesthesiologist-guided environment.

Although we did not study the impact of ED clinical pharmacists on the safe practice of pediatric procedural sedation, pharmacists can be utilized to oversee and ensure the safe administration of conscious-altering medications. During our study, the ED clinical pharmacist gained considerable experience in the choice, dose, and titration of agents along with the discernment and differentiation of the major and minor AEs. The pharmacist also helped educate the parents/caregiver and child on what to anticipate in terms of therapeutic effects and AEs of the agent(s) used during procedural sedation. Because the ED clinical pharmacist was present during the procedures, he/she provided dosage recommendation and drug information to practitioners, ensuring that a correct drug and dose were given.

Over the course of the study, we noted an increased move to use ketamine, which could be correlated with an increased presence of ED clinical pharmacists as

well as EM physicians' increased comfort level with certain medications. However, given the high turnover of medical residents at a teaching hospital, ED clinical pharmacists, who are a permanent fixture in our ED, can ensure that future procedures are executed in a safe manner and work together with medical staff in a combined effort to maximize patient safety.

CONCLUSION

EM-trained physicians can safely perform pediatric procedural sedation in the ED. In the ED, the most common procedure requiring conscious sedation is fracture reduction with ketamine as the preferred agent. ED clinical pharmacists can facilitate the selection and preparation of medications to ensure the safety of pediatric procedural sedation.

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APPENDIX A

Data Collection Sheet

Allocation #
Sex
Age
Height
Weight
Procedure
Length of procedure
Supplemental oxygen
Physician
Agent #1
Dose (milligrams/kilogram) AND route
Time from administration to onset of sedation
Duration of sedation (minutes)
Side effects
Ramsay Scale
Agent #2
Dose (milligrams/kilogram) AND route
Time from administration to onset of sedation
Duration of sedation (minutes)
Side effects
Ramsay Scale
Agent #3
Dose (milligrams/kilogram) AND route
Time from administration to onset of sedation
Duration of sedation (minutes)
Side effects
Ramsay Scale

APPENDIX B**Table B1.** Medication reactions

Body system	Medication reactions
Body as a whole	Shivering, itching, tingling, fatigue
Cardiovascular	Hypertension, tachycardia
Digestive	Salivation, vomiting
Central nervous system	Dizziness, ataxia
Ocular	Nystagmus, lacrimation, diplopia, blurry vision
Neuromuscular and skeletal	Tonic-clonic movements, restless legs, tremor
Respiratory	Hypoxia, apnea, tachypnea
Skin	Injection site reaction, rash, facial flushing
Urogenital	Urinary urgency, urinary incontinence
Miscellaneous	Vocalization, grimace, hiccups, agitation, dysphoric emergence, confusion, yawning, protruding tongue, sneezing

APPENDIX B**Table B2.** Number of medication reactions with ketamine

Route of ketamine administration (n = 144)	n (%) ^a	Medication reactions (no. events per patient) ^b
Intravenous	91 (46)	135 (1.5)
Intramuscular	49 (25)	86 (1.8)

^aPercent of total patients in study receiving only ketamine.

^bFour patients were excluded because intramuscular ketamine was initially administered, followed by intravenous ketamine due to inadequate sedation.