

## CLINICAL PRACTICE

# Adverse Events Associated with Procedural Sedation and Analgesia in a Pediatric Emergency Department: A Comparison of Common Parenteral Drugs

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## Abstract

**Objectives:** To compare the frequency and severity of adverse events associated with parenteral drugs commonly used for procedural sedation and analgesia (PSA) in a pediatric emergency department. **Methods:** A database of consecutive patients receiving parenteral PSA was prospectively generated with the intent of monitoring safety in the emergency department. Data were logged onto a dedicated sedation sheet. A retrospective analysis was performed; comparisons were made based on sedation drugs used. **Results:** A total of 2,609 patients from June 1, 1996, to September 16, 2003, received PSA by emergency physicians. Patients who received PSA nonparenterally ( $n = 109$ ) were excluded. A total of 2,500 patients (2,279, intravenous; 221, intramuscular) remained for analysis. Age range was 19 days to 32 years (median, 6.7 years). A total of 1,511 (60.4%) were male. Four major drug combinations were identified: ketamine alone ( $n = 1,492$ ; 59.7%), ketamine/midazolam ( $n = 299$ ; 12.0%), midazolam/fentanyl ( $n = 336$ ; 13.4%), and midazo-

lam alone ( $n = 260$ ; 10.4%). A total of 113 patients (4.5%) received various other combinations of drugs. A total of 458 adverse events were observed in 426 patients (17%). Respiratory adverse events occurred as follows: ketamine alone, 91 patients (6.1%); ketamine/midazolam, 30 patients (10%); midazolam/fentanyl, 65 patients (19.3%); midazolam alone, 15 patients (5.8%). Vomiting occurred as follows: ketamine alone, 151 patients (10.1%); ketamine/midazolam, 16 patients (5.4%); midazolam/fentanyl, six patients (1.8%); midazolam alone, two patients (0.8%). **Conclusions:** Drug types used in pediatric PSA are associated with different adverse event profiles. Patients receiving ketamine with or without midazolam experienced fewer respiratory adverse events but more vomiting than the commonly used combination of midazolam and fentanyl. Adverse events may occur in any patient receiving parenteral PSA. **Key words:** pediatrics; sedation; adverse events. *ACADEMIC EMERGENCY MEDICINE* 2005; 12:508–513.

Several recent studies have attempted to identify risk factors for adverse events associated with procedural sedation and analgesia (PSA).<sup>1–5</sup> Coté et al. found the following to be associated with adverse events and poor outcome: sedation performed in an out-of-hospital-based setting, sedation administered with inadequate monitoring, lack of adequate pre-sedation evaluation, lack of standard recovery procedures, and medication errors and lack of an independent observer.<sup>1</sup> In several studies, factors such as age, gender, type of drugs or route of administration, and length of preprocedural fasting have not been shown to significantly impact on the incidence or severity of adverse events.<sup>1–3,5–7</sup>

Contrary to the above reports, a study comparing fentanyl/midazolam with ketamine/midazolam for orthopedic procedures found that ketamine/midazolam was more effective for pain and anxiety relief and produced fewer respiratory complications than fentanyl/midazolam.<sup>8</sup> In addition, a large cohort study found that patients receiving intravenous fentanyl/midazolam were significantly more likely to experience a complication during PSA, while patients sedated using intravenous ketamine, midazolam, and atropine or midazolam alone were less likely to experience a complication during PSA.<sup>5</sup>

The most commonly used drugs in our emergency department (ED) for PSA are ketamine (with or without midazolam), midazolam/fentanyl, and midazolam alone. The objective of this study was to compare the frequency and severity of adverse events associated with parenteral drugs commonly used for PSA in a pediatric ED.

## METHODS

**Study Design.** This study was a retrospective analysis of a cohort of consecutive ED pediatric patients who received parenteral PSA. Sedation data were prospectively logged onto a sedation sheet that becomes part of

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Received August 8, 2004; revisions received November 11, 2004, and December 9, 2004; accepted December 9, 2004.

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doi:10.1197/j.aem.2004.12.009

the medical record. This database was generated for the purpose of investigating adverse events associated with PSA and the effects of commonly used sedation drugs. The primary outcome measure was incidence of adverse events. This study was approved as an exempt protocol by the Colorado Multiple Institutional Review Board.

**Study Setting and Population.** This study was performed in the ED of an urban, tertiary care children's teaching hospital that averages 47,000 patient visits per year. Patient sedation data were collected from June 1996 to September 2003. Patients receiving parenteral PSA in the ED by attending emergency physicians were included. Patients who received sedation administered by routes other than intravenous or intramuscular were excluded. Other aspects of these sedation data have been described in previous publications.<sup>7,9</sup>

**Study Protocol.** This was an observational study of consecutive ED patients receiving PSA. No study interventions were made. Drugs administered and procedures performed were determined by the attending emergency physician. All patients receiving sedation and their guardians were informed of the risks and benefits of PSA by the attending physician, who obtained verbal consent. Patients were monitored with continuous pulse oximeter and cardiorespiratory monitors. Blood pressure measurements were recorded every five minutes by a nurse who had completed a presedation assessment and was at the bedside from the time of administration of the sedation drug to the time the patient was ready for discharge. Adverse events were recorded on the sedation sheets in a box labeled "complications." This box contained checkboxes for "no" if none occurred and "yes" followed by three blank lines to list the adverse events that occurred. The narrative and graphical (heart rate, respiratory rate, blood pressure, and oxygen saturation) sections of the form were also reviewed for adverse events. All attending physicians who administered sedation drugs were credentialed by the hospital to provide ED sedation.

**Measurements.** For all patients receiving PSA in this ED, sedation sheets, which are used hospital-wide and become part of the medical record, are automatically generated. Nurses and physicians caring for the patients complete these sedation sheets. Sedation sheets are collected and reviewed quarterly as a hospital quality assurance initiative. For the purpose of this study, data pertaining to procedure type, drugs used, and adverse events were abstracted from the sedation sheet only. A nurse who functions as the ED research coordinator and who was not a study investigator abstracted data from the sedation sheets.

No further chart review occurred. Adverse events routinely assessed were bradycardia, hypotension, oxygen desaturation, apnea, laryngospasm, nausea, vomiting, rash, increased muscle tonicity/rigidity, and seizures. Oxygen desaturation was defined as a pulse oximeter reading <90% (elevation, 5,280 ft).

**Data Analysis.** For the purposes of data analysis, we treated adverse events as categorical, dichotomous variables. We used SPSS version 12.0 (SPSS Inc., Chicago, IL) to analyze for differences in the percentage of patients having adverse events between drug groups. To analyze for differences in adverse event rates by drug type, we calculated simple odds ratios with 95% confidence intervals using ketamine alone as our reference group.

## RESULTS

During the study period, 2,609 patients received PSA in the ED. Patients who received PSA nonparenterally ( $n = 109$ ) were excluded. A total of 2,500 patients (2,279, intravenous; 221, intramuscular) remained for analysis. Age range was 19 days to 32 years (median, 6.7 years). A total of 1,511 (60.4%) were male. Four major drug combinations were identified: ketamine alone ( $n = 1,492$ ; 59.7%), ketamine/midazolam ( $n = 299$ ; 12.0%), midazolam/fentanyl ( $n = 336$ ; 13.4%), and midazolam alone ( $n = 260$ ; 10.4%). All patients who received ketamine alone or ketamine/midazolam also received the antisialagogue glycopyrrolate. A total of 113 patients (4.5%) received various other combinations of drugs. Table 1 lists the demographics of these patients by drugs received and procedure performed. Four patients were older than 21 years of age. Three of these patients had congenital heart disease and received PSA for cardioversion. One experienced brief oxygen desaturation treated with blow-by oxygen only. Table 2 lists all procedures performed.

From the sedation sheets, a total of 458 adverse events were identified in 426 patients (17%). The complications box on the sedation forms was left blank for 266 patients (10.6%). From the narrative and graphical sections of the sedation form, three additional complications were identified in these patients. These complications were desaturation (2) and seizure (1). Further review of the narrative and graphical sections of the sedation form in all patients identified three patients with complications in whom the "no" complications box had been checked. Two of these patients experienced nausea and one a rash.

Respiratory adverse events and vomiting were the most common adverse events occurring in 374 patients (15.0%). A respiratory adverse event was observed in 214 patients (8.6%), and vomiting occurred in 181 patients (7.2%). Respiratory adverse events were most common in the midazolam/fentanyl group (19.3%). Using ketamine alone as the reference group,

**TABLE 1. Sedation Drugs and Procedure Types**

	Ketamine Alone	Ketamine/Midazolam	Midazolam/Fentanyl	Midazolam Alone	Other*
No. of patients (%)	1,492 (59.7)	299 (12.0)	336 (13.4)	260 (10.4)	113 (4.5)
Median age, yr (range)	6.85 (39 d to 22 y)	6.21 (4.8 mo to 18 y)	7.84 (19 d to 28 y)	4.91 (42 d to 32 y)	5.57 (30 d to 18 y)
Gender (% male)	63.1	56.9	56.8	52.7	62.8
Procedure (%)					
Fracture reduction	65.5	59.5	28.3	4.6	27.4
Laceration repair	18.8	26.8	17.0	13.1	10.6
Lumbar puncture	0.7	1.7	20.5	34.6	18.6
Imaging	0.7	2.0	3.6	24.6	16.8
Other	14.3	10.0	30.6	23.1	26.6

\*Other drug combinations were as follows: midazolam/morphine (36), fentanyl (21), pentobarbital (11), ketamine/fentanyl (10), midazolam/ketamine/fentanyl (9), morphine/ketamine (8), midazolam/fentanyl/morphine (4), midazolam/ketamine/pentobarbital (3), midazolam/ketamine/morphine (3), midazolam/pentobarbital (2), lorazepam (1), ketamine/meperidine (1), midazolam/fentanyl/pentobarbital (1), midazolam/morphine/diazepam (1), fentanyl/morphine (1), and fentanyl/morphine/diazepam (1).

patients receiving midazolam/fentanyl were more likely to experience a respiratory adverse event. Vomiting was most common in the ketamine alone group (10.1%) (Table 3).

Patients with a respiratory adverse event experienced oxygen desaturation <90%, apnea, or laryngospasm. Patients were considered to have apnea if the sedation form listed apnea or a cessation in breathing that resulted in a verbal cue, tactile stimulation, or bag-mask ventilation. Laryngospasm was listed as a complication if the sedation form listed laryngospasm or stridor that did not resolve with a simple intervention such as positioning or jaw thrust. Apnea occurred in 19 (0.8%) and laryngospasm in three (0.1%) of the 2,500 patients receiving PSA. All patients experiencing apnea or laryngospasm were managed with the

administration of oxygen, breathing cues, airway positioning, or bag-mask ventilation. No patients in this study received endotracheal intubation secondary to PSA, and no reversal drugs were administered. A breakdown of apnea and laryngospasm by drug type is listed in Table 4.

Laceration repair was the only procedure in which significant numbers of all four drug regimens were represented. Respiratory adverse events and vomiting occurring during laceration repair are listed in Table 5 by drug type used. The rates of respiratory adverse events and vomiting by drugs used with laceration repair alone were similar to those reported when all procedures were considered (Table 3).

Bradycardia from 40 to 50 beats/min occurred in one patient receiving midazolam/fentanyl for a radiographic procedure. The bradycardia was not associated with desaturation and resolved without intervention. One 4-year-old patient who had received ketamine experienced transient hypotension (82/33 mm Hg) after vomiting. This event was attributed to a vagal response to vomiting; it responded spontaneously, and the patient received no additional treatment. Arrhythmias were not observed.

Other adverse events observed were rash (43), nausea (11), hypertonicity/muscle rigidity (2), and intravenous infiltration (1). Four patients were reported to have seizures. Three of these patients received ketamine, and one received ketamine and fentanyl. One patient had an underlying seizure disorder being treated with topiramate. Three of the seizures, including one reported in the patient with a seizure disorder, were described as "muscle shaking" or "muscle stiffening," which resolved without intervention. In the patient who received ketamine and fentanyl, the seizure was described as "generalized tonic-clonic." This patient received midazolam, at which time the episode resolved. This patient also experienced desaturation after receiving midazolam. In the other patients reported to have had a seizure, no other adverse event occurred.

**TABLE 2. Complete Procedure List**

Procedures	n
Fracture reduction/dislocation	1,294 (51.8%)
Laceration repair	463 (18.5%)
Lumbar puncture	194 (7.8%)
Radiology	111 (4.4%)
Incision and drainage	81 (3.2%)
Genital/urinary procedure	47
Orthopedic/other	46
Chest tube/thoracostomy	43
Joint aspiration	30
Wound care	26
Burn dressing	24
Foreign body removal	23
Eye examination	21
Gastrointestinal procedure	21
Dental procedure	19
Line manipulations	18
Echocardiogram	10
Ear/nose/throat	9
Cardiac procedure	8
Other	12*
<b>Total</b>	<b>2,500</b>

\*Other procedures performed were as follows: ventriculoperitoneal shunt tap (5), bone marrow biopsy (4), lymph node biopsy (2), and lymphangioma excision (1).

**TABLE 3. Adverse Events by Drug Type**

Sedation Drugs	Respiratory Adverse Events <i>n</i> (%); OR (95% CI)	Vomiting <i>n</i> (%); OR (95% CI)
Ketamine alone ( <i>n</i> = 1,492) (reference group)	91 (6.1); 1	151 (10.1); 1
Ketamine/midazolam ( <i>n</i> = 299)	30 (10); 1.72 (1.11, 2.65)	16 (5.4); 0.50 (0.30, 0.85)
Midazolam/fentanyl ( <i>n</i> = 336)	65 (19.3); 3.70 (2.62, 5.21)	6 (1.8); 0.16 (0.07, 0.37)
Midazolam ( <i>n</i> = 260)	15 (5.8); 0.94 (0.54, 1.66)	2 (0.8); 0.07 (0.02, 0.28)
Other drugs/combinations ( <i>n</i> = 113)	13 (11.5); 2.00 (1.08, 3.70)	6 (5.3); 0.50 (0.22, 1.15)

No patients were admitted to the hospital secondary to adverse events associated with PSA, and no patients were reported to have experienced clinically apparent pulmonary aspiration.

## DISCUSSION

In contrast to several previous studies, we found specific sedation drug regimens to be associated with different adverse event profiles.<sup>1-3,6</sup> This may be due to the fact that this study investigated a larger number of patients than those previous studies and that all drugs were administered parenterally. Two recent studies investigated adverse events associated with PSA in large numbers of pediatric patients.<sup>3,5</sup> As previously mentioned, Pitetti et al. found the combination of midazolam/fentanyl to be more likely to result in adverse events, specifically respiratory ones.<sup>5</sup> Our data support this finding, which is consistent with a previous randomized, controlled trial of midazolam/fentanyl versus ketamine/midazolam.<sup>8</sup> We also found a greater incidence of vomiting associated with ketamine with or without midazolam as compared with midazolam/fentanyl or midazolam alone. These findings are similar to those in the two studies described here.<sup>5,8</sup>

The overall incidence of respiratory adverse events and vomiting in this study (15%) is similar to that of Pitetti et al. (17.9%)<sup>5</sup> but significantly higher than that found by Pena and Krauss (2.3%).<sup>3</sup> As mentioned by Pitetti et al., the patients in the study by Pena and Krauss received different drugs and a lower oxygen saturation cutoff (90% at sea level) was used to define a respiratory adverse event. This may have contributed to the lower complication rate.

**TABLE 4. Apnea and Laryngospasm by Drug Type Administered**

	Apnea	Laryngospasm
Ketamine alone ( <i>n</i> = 1,492)	11 (0.7%)	1 (0.07%)
Ketamine/midazolam ( <i>n</i> = 299)	3 (1.0%)	0
Midazolam/fentanyl ( <i>n</i> = 336)	3 (0.9%)	0
Midazolam alone ( <i>n</i> = 260)	0	0
Other ( <i>n</i> = 113)	2*	2†

\*One patient received midazolam and morphine, and a second received ketamine, midazolam, and morphine.

†One patient received ketamine, midazolam, and fentanyl, and a second received midazolam, fentanyl, and morphine.

Due to the large number of patients receiving ketamine alone and ketamine/midazolam in our study, we are able to offer further information about the differences of adverse events between ketamine alone and ketamine/midazolam. Previous studies have commented on the inability of midazolam to diminish emergence reactions associated with ketamine sedation.<sup>9,10</sup> Wathen et al. commented further that in their 266 patients, those who received ketamine/midazolam were more likely to have oxygen desaturation but less likely to vomit than those receiving ketamine alone.<sup>9</sup> As mentioned in Methods, other aspects of these sedation data have been described in previous publications.<sup>7,9</sup> Two hundred and sixty-six patients from the study by Wathen et al. are included in our database, representing 36% of our patients receiving ketamine/midazolam and 9% of our patients receiving ketamine alone. When the patients in the study by Wathen et al. are removed from our data set, we have 162 patients receiving ketamine/midazolam and 1,363 patients receiving ketamine alone who displayed similar results, with more respiratory adverse events and less vomiting in the ketamine/midazolam group when compared with ketamine alone.

The antiemetic properties of midazolam and other benzodiazepines have been previously described for patients in the perioperative period and in those receiving chemotherapy.<sup>11-13</sup> In their letter to the editor, Kennedy and McAllister postulated that despite findings to the contrary, certain subsets of patients, such as those with significant preprocedural agitation, may benefit from concurrent midazolam during ketamine sedation.<sup>14</sup> They also commented that little is known about the medium- to long-term sequelae of ED ketamine sedation and question whether the amnestic properties of midazolam may be beneficial.

When data from the studies by Wathen et al. and Sherwin et al., as well as from the study presented here, are considered, it seems that the benefits of the addition of midazolam to ketamine sedation for the majority of patients may be limited to a decrease in vomiting. Due to the increase in respiratory adverse events observed when ketamine is combined with midazolam, it would seem that an alternative strategy for emesis control for ketamine sedation should be investigated. Other potential benefits of concurrent administration of midazolam remain to be elucidated.

**TABLE 5. Respiratory Adverse Events and Vomiting by Drug Type for Patients Undergoing Laceration Repair**

Laceration Repair (n = 451)	Respiratory Adverse Events n (%); OR (95% CI)	Vomiting n (%); OR (95% CI)
Ketamine alone (n = 280) (reference group)	18 (6.4); 1	31 (11.1); 1
Ketamine/midazolam (n = 80)	9 (11.3); 1.85 (0.80, 4.28)	9 (11.3); 1.02 (0.46, 2.24)
Midazolam/fentanyl (n = 57)	12 (21.1); 3.88 (1.75, 8.60)	2 (3.5); 0.29 (0.07, 1.26)
Midazolam alone (n = 34)	0 (0); 0	1 (2.9); 0.24 (0.03, 1.84)

Cardiovascular adverse events were uncommon in this study, occurring in two patients of 2,500 (0.001%); one patient experienced bradycardia, and one had transient hypotension. These findings are consistent with those of Pitetti et al. (two episodes of hypotension in 1,244 sedations; 0.002%)<sup>5</sup> and Pena and Krauss (one episode of bradycardia in 1,180 sedations; 0.001%).<sup>3</sup> Tachycardia and hypertension are expected effects of ketamine sedation and were not recorded as complications.<sup>15,16</sup> Neither tachycardia nor hypertension occurred in any of the other drug groups.

Muscular hypertonicity has been reported to occur commonly with ketamine sedation and was observed in two patients receiving ketamine sedation in this study.<sup>15,17,18</sup> Seizure activity with ketamine, however, has only been reported rarely.<sup>19,20</sup> Given that ketamine is reported to actually have anticonvulsant properties,<sup>15,16,21</sup> it would seem appropriate that our report of seizures in four patients receive closer scrutiny. Only one patient was described as having generalized tonic-clonic-type movement. It is quite possible that the “shaking episodes” described to have occurred in these patients may have been exaggerated muscular hypertonicity rather than true seizure activity.

This study identified adverse events in 17% of patients receiving parenteral PSA. Furthermore, 15% of patients experienced either a respiratory adverse event or vomiting. These adverse events were singled out due to their common occurrence and concern that vomiting and respiratory adverse events could lead to more serious complications, such as clinically apparent aspiration. While aspiration did not occur in this patient population, advanced airway maneuvers, including bag-mask ventilation, were used for some patients.

According to our findings, significant numbers of pediatric patients receiving ED parenteral PSA with the drugs listed here will experience a respiratory adverse event or vomiting. Furthermore, although uncommon, patients will also experience apnea or laryngospasm. It is important to note that despite these adverse events, no patients experienced significant morbidity associated with PSA. These data serve to emphasize that all patients receiving PSA must be properly monitored and attended to by personnel skilled in airway and breathing management.

## LIMITATIONS

The study had several limitations. Trained nursing observers who recorded data were not blinded to the

type of sedation used, which could lead to bias in reporting. Those observers were, however, blinded to the research study objective. Multiple observers were used, and interrater variability was not calculated. Also, depth of sedation was not assessed, which could have been associated with certain adverse events and may provide more information about the true cause of these events.

This was an observational study. Sedation drugs administered for specific procedures were chosen by the attending emergency physicians on a case-by-case basis. The lack of randomization is the main source of possible bias in this study. Randomizing patients to sedation drugs and controlling for procedure type may have provided us with a more accurate description of the association between adverse events and specific sedation drug regimens. However, this would have limited the number of subjects enrolled and would not have accurately reflected our ED practice. As practitioners, we choose certain drug regimens preferentially for certain procedures (Table 1).

To address the issue of bias, we compared respiratory adverse events and vomiting by drug group for laceration repair (see Table 5). We found results similar to those found when all procedures were considered, supporting our finding that patients receiving midazolam/fentanyl are more likely to experience a respiratory adverse event and those receiving ketamine with or without midazolam are more likely to vomit.

## CONCLUSIONS

Individual drug regimens used in pediatric PSA are associated with different adverse event profiles. Ketamine, with or without midazolam, was associated with fewer respiratory adverse events but more vomiting than the commonly used combination of midazolam and fentanyl. The addition of midazolam to ketamine reduced vomiting but also resulted in an increase in respiratory adverse events. All patients receiving parenteral PSA are at risk for adverse events, necessitating the use of appropriate monitoring and administration by trained personnel.

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