Comparison of Fentanyl/Midazolam With Ketamine/Midazolam for Pediatric Orthopedic Emergencies

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ABSTRACT. *Objective.* **Emergency management of pediatric fractures and dislocations requires effective analgesia, yet children's pain is often undertreated. We compared the safety and efficacy of fentanyl- versus ketamine- based protocols.**

Methodology. **Patients 5 to 15 years of age needing emergency fracture or joint reduction (FR) were randomized to receive intravenous midazolam plus either fentanyl (F/M) or ketamine (K/M). Measures of efficacy were observational distress scores and self- and parental-report. Measures of safety were frequency of abnormalities in and need for support of cardiopulmonary function and other adverse effects.**

Results. **During FR, K/M subjects ($n = 130$) had lower distress scores and parental ratings of pain and anxiety than did F/M subjects ($n = 130$). Although both regimens equally facilitated reductions, deep sedation, and procedural amnesia, orthopedists favored K/M. Recovery was 14 minutes longer for K/M.**

Fewer K/M subjects had hypoxia (6% vs 25%), needed breathing cues (1% vs 12%), or required oxygen (10% vs 20%) than did F/M subjects. Two K/M subjects required assisted ventilation briefly. More K/M subjects vomited. Adverse emergence reactions were rare but equivalent between regimens.

Conclusions. **During emergency pediatric orthopedic procedures, K/M is more effective than F/M for pain and anxiety relief. Respiratory complications occurred less frequently with K/M, but respiratory support may be needed with either regimen. Both regimens facilitate reduction, produce amnesia, and rarely cause emergence delirium. Vomiting is more frequent and recovery more prolonged with K/M.** ***Pediatrics*** **1998;102:956–963;** ***ketamine, fentanyl, midazolam, pediatric procedure sedation.***

ABBREVIATIONS. ED, emergency department; F/M, fentanyl/midazolam; K/M, ketamine/midazolam; FR, fracture reduction/joint relocation; ASA, American Society of Anesthesiologists; FAS, Facial Affective Scale; VAS, Visual Analog Scale; OSBD–R, Observational Scale of Behavioral Distress–Revised; BVM, bag-valve-mask.

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Fractures and joint dislocations are among the most painful pediatric emergencies. Successful management in the emergency department (ED) requires effective relief of pain and anxiety. However, compared with adults with similar injuries, children receive less medication for pain.[1–6] Reasons for inadequate sedation and analgesia include lack of consensus about optimal medications[6–14] and monitoring,[11] lack of physician familiarity with dosing, and fear of adverse effects of potent medications.[15,16]

A popular regimen for ED sedation and analgesia combines the high potency opioid fentanyl and the benzodiazepine midazolam (F/M).[7,17,18] Respiratory depression associated with this regimen[17–19] has prompted concern.[17,20] Recent reports on use of the dissociative anesthetic ketamine alone[21–24] or in combination with midazolam (K/M)[25,26] for less painful pediatric procedures indicate marked sedation without major respiratory complications or emergence dysphoria.

The purpose of this study was to compare the efficacy and safety of fentanyl with ketamine for sedation and analgesia for painful orthopedic fracture reduction/joint relocation (FR) in the ED. Midazolam was used as an adjunct to both agents to increase amnesia[25,27–30] and to decrease anxiety[27,28] and emergence delirium.[31,32]

METHODS

Subjects

St Louis Children's Hospital ED patients between 5 and 15 years of age requiring FR and meeting American Society of Anesthesiologists (ASA) class I or II criteria[33] were invited to participate in the study between June 1, 1993, and December 31, 1994.

Exclusion criteria were abnormalities of airway, cardiorespiratory, hepatic, renal, or central nervous systems; history of psychoses; ethanol, psychotropic, or nonprescribed narcotic drug use within 6 hours of the procedure; and adverse reaction to the study drugs, opiates, or benzodiazepines.

Demographic data, fracture locations, and frequency of successful ED reductions were recorded for patients who were eligible but not enrolled. Washington University School of Medicine's institutional review board approved the research protocol, study design, and consent forms.

Protocol

All reductions and recoveries were performed in an ED treatment room fully equipped for monitoring, resuscitation, and audiovisual recording. After informed consent was obtained, videotaping of subjects began and continued until discharge. Subjects were stratified according to initial parental choice to remain in the room (IN) or not (OUT) during reduction. Parents were later allowed to change their location. Subjects completed a nine-point Facial Affective Scale (FAS) on which decimal scores ranged from

0 to 1, with higher scores indicating greater distress.[34] Parents completed a 10-point visual analog scale (VAS)[35] questionnaire to rate subjects' and parents' usual anxiety and ability to handle pain compared with those of peers, and parents' anxiety and expectations of subjects' pain during reduction; higher scores indicated greater coping skills or greater anxiety or pain.

Subjects were randomly assigned in blocks of 20 within strata to receive fentanyl or ketamine. Randomization sequences were predetermined by a random number generator and maintained in sealed envelopes until consent was obtained. For subject safety and because study medications effects are clinically distinguishable, sedators were not blinded to medication regimens.

All medications were administered by attending emergency pediatricians or fellows (23 sedators) familiar with study medications and protocol. Sedators observed subjects directly throughout sedation and reduction periods and until adequate cardiopulmonary functions were verified during recovery. Registered nurses remained with subjects throughout sedation, reduction, and recovery periods. Orthopedic surgery residents who rated their satisfaction with sedation on a 10-point VAS performed reductions.

Before and throughout sedation, levels of consciousness,[36] standard cardiopulmonary functions, oxygen saturations, and end-tidal Co_2 levels were monitored continuously using a SpaceLabs model PC-2 monitor and documented by the nurse at 5-minute intervals or 3 minutes after each medication bolus and at the time of any significant clinical change. After reduction, when subjects' cardiopulmonary functions were determined to be stable and adequate, documentation intervals were increased to 10 minutes until discharge. Also documented were subjects' age, weight, sex, race, fracture type, ASA classification, allergies, time of last oral intake and presedation medications administered to the patient; medication doses and administration times; descriptions and times of adverse effects and interventions; and times of reductions.

Criteria for discharge were normal cardiopulmonary function; return to presedation level of responsiveness; and ability to talk, drink, and sit unaided and to walk with minimal assistance.[36] At discharge, subjects completed a second FAS and parents completed VAS questionnaires to rate subjects' pain during reduction and their own and subjects' anxiety during and after reduction. Subjects were asked what they remembered about the reduction. Parents completed questionnaires at 1 and 7 days after reduction to assess subjects' symptoms. Parents who failed to return questionnaires were contacted by telephone.

Medications

Medications were administered over 10 to 20 seconds at the hub of standard intravenous catheters. Based on previous work,[18] study medication titration doses were chosen to minimize adverse respiratory effects yet to efficiently achieve sedation and analgesia. Administered doses were determined from precalculated tables based on subject weight and standardized medication concentrations (midazolam, 1 mg/mL; fentanyl, 10 μg/mL; ketamine, 10 mg/mL). At sedators' discretion, doses were titrated to achieve desired clinical effects.

Midazolam

All subjects initially received midazolam $\leq$0.1 mg/kg (maximum, 2.5 mg) every 3 minutes until speech slurred or eyes became glassy or until a maximum first reduction dose of 0.3 mg/kg (maximum, 7.5 mg) had been administered.

Fentanyl

At least 1 minute after midazolam was administered, F/M subjects received fentanyl $\leq$0.5 μg/kg every 3 minutes until a decreased response to verbal or painful stimuli occurred or a maximum first reduction dose of 2 μg/kg (maximum, 100 μg) had been administered.

Ketamine

K/M subjects received the antisialagogue glycopyrrolate (5 μg/kg; maximum, 250 μg). At least 1 minute after midazolam was administered, K/M subjects received ketamine $\leq$0.5 mg/kg every 3 minutes until a decreased response to verbal or painful stimuli occurred or a maximum first reduction dose of 2 mg/kg had been administered.

If sedators determined analgesia or sedation was insufficient for the first reduction attempt or if additional reduction attempts were necessary, additional midazolam and/or original study drug were administered. If significant adverse effects from study medications occurred and/or sedation and analgesia were insufficient for reduction, the subject was considered a treatment failure and other analgesics were administered or reduction was performed under general anesthesia. Fractures requiring open reduction or mechanical fixation were not considered treatment failures.

Quantification of Distress

The primary outcome measure for efficacy was the Observational Scale of Behavioral Distress-Revised (OSBD–R).[37,38] Secondary measures were FAS scores, parent VAS ratings of subjects' pain and anxiety during reduction, and subjects' amnesia for reduction.

One of two trained observers who were blinded to study purpose and design reviewed the videotape of each study. Each tape was scored using the OSBD–R, which has been validated for children of ages within our sample range. The presence of each of eight behaviors (cry, scream, restraint, verbal resistance, emotional support, verbal pain, and flail) was noted every 15 seconds during the following intervals: iv insertion, presedation (3 minutes before first dose of midazolam), reduction (all reduction attempts), and discharge (3 minutes before discharge). Interrater reliability was assessed before scoring study tapes and midway during the scoring process. κ Coefficients ranged from .65 to 1.0 on a sample of five tapes at the midway point.

Statistical Analysis

Primary data analysis for efficacy compared mean reduction OSBD–R scores for the K/M and F/M groups using *t* tests. Calculations of sample size, mean, and SD were based on estimates provided by the OSBD–R author (S.M. Jay, personal communication, 1993). Assuming that the population means OSBD–R was 1.75 $\pm$ 1.85 (data from oncology patients undergoing lumbar puncture) with power of .80 and α of .05, a change in the mean of 1.05 could be detected with a sample of 40 children in each treatment group. To calculate sample size for safety, an incidence of adverse events was estimated to be 13% for F/M[18] and 3.5% for K/M.[32] To detect the difference between these two proportions, with power of .80 and α of .05, a sample size of 100 children in each group was needed.

t tests were used for continuous variables and χ^2 tests, or Fisher's exact tests (for small cell sizes) for categorical variables. *t* tests were used to examine the effect of parental location (initial intent) on OSBD–R scores and on parents' VAS ratings. Eligible but not enrolled subjects were compared with enrolled subjects by age, sex, race, fracture location, and frequency of successful ED reduction to assess for bias in enrollment. All statistical analyses were performed using SAS (SAS Institute, Carey, NC) with $P < .05$ taken as statistically significant.

RESULTS

Baseline Characteristics

A total of 130 subjects (80% of eligible) were assigned to each medication regimen. Of the subjects whose parents initially choose to remain IN, 84/167 were assigned to F/M, and 46/93 whose parents remained OUT were assigned to F/M. F/M and K/M groups did not differ in mean age, weight, gender, race, ASA class, time from last oral intake, fracture location, or presedation medications (Table 1). The 66 patients meeting eligibility criteria but not enrolled because of lack of parental consent or videotaping resources at the time of presentation did not differ from study subjects by mean age, sex, race, fracture location, or frequency of successful reduction.

There were no differences between groups (F/M vs K/M) for mean parental ratings of subjects' usual

TABLE 1. Subject Characteristics

	Fentanyl/Midazolam (n = 130)	Ketamine/Midazolam (n = 130)	P Value
Parents in Treatment Room			
Original intent (%)	84 (65)	83 (64)	.90
Actual location (%)[a]	65 (50)	60 (46)	.54
Age, y[b]	9.7 ± 3.01	9.7 ± 3.27	.78
Weight, kg[b]	40.1 ± 15.5	40.6 ± 17.6	.80
Male (%)	94 (72)	88 (68)	.41
Black (%)	64 (49)	59 (45)	.52
ASA class I (%)[c]	108 (83)	102 (78)	.35
Hours between last oral			
Intake and sedation[b]	5.2 ± 2.6	4.8 ± 2.3	.19
Injury site (%)[d]			
Upper arm fracture	8 (6)	6 (5)	
Lower arm fracture	100 (75)	99 (75)	
Upper leg fracture	11 (8)	10 (8)	
Lower leg fracture	11 (8)	13 (10)	
Shoulder dislocation	0 (0)	1 (1)	
Elbow dislocation	3 (2)	3 (2)	
Presedation medications (%)			
Parenteral opiates[e]	28 (22)	38 (29)	.20
Parenteral sedatives[f]	2 (2)	0 (0)	.50
Other[g]	8 (6)	8 (6)	1.00

[a] Parents were allowed to change choice of location during reduction after initial stratification.
[b] Mean ± SD.
[c] American Society of Anesthesiologists (ASA) criteria.[33]
[d] More than 1 site per patient possible.
[e] Morphine (F/M = 19, K/M = 25), mepridine (F/M = 8, K/M = 13), fentanyl (F/M = 1, K/M = 0).
[f] Midazolam (F/M = 2, K/M = 0).
[g] Acetaminophen with codeine (F/M = 1, K/M = 2), ibuprofen (F/M = 2, K/M = 1).

anxiety (5.90 ± 2.70 vs 5.61 ± 2.53; P = .36) or ability to handle pain (6.09 ± 3.11 vs 6.29 ± 2.58; P = .58), mean OSBD–R scores during iv insertion (1.01 ± 1.34 vs .89 ± 1.26; P = .66) or presedation (.28 ± .59 vs .20 ± .38; P = .26), or in mean parental self-estimates of usual anxiety (5.94 ± 2.87 vs 5.70 ± 2.72; P = .47), ability to handle pain (6.52 ± 3.24 vs 6.98 ± 2.80; P = .21), anxiety about reduction (6.43 ± 3.14 vs 6.45 ± 3.11; P = .99), or pain expected in subject during reduction (7.44 ± 2.77 vs 6.90 ± 2.99; P = .14). K/M subjects, however, had lower mean presedation FAS scores compared with F/M subjects (0.65 ± .27 vs 0.71 ± .21; P = .03).

Efficacy

During reduction, K/M subjects had lower OSBD–R scores than did F/M subjects (1.08 ± 1.12 vs 2.70 ± 2.16; $P \leq .0001$) (Fig 1). Parental ratings of subjects' pain (P = .004) and anxiety (P = .02) also were lower (Table 2). Parents' location (original intent, IN vs OUT) was not related to mean reduction OSBD–R scores (1.73 ± .15 vs 1.80 ± .23; P = .81) or parental VAS estimates of subjects' reduction pain (4.82 ± .30 vs 4.86 ± .44; P = .94) or anxiety (4.73 ± .28 vs 5.13 ± .42; P = .43). At discharge, for F/M versus K/M, FAS scores (.38 ± .27 vs .36 ± .27; P = .56), OSBD–R scores (.21 ± .56 vs .28 ± .57; P = .36) and subjects' anxiety (3.87 ± 3.04 vs 4.19 ± 3.20; P = .48) did not differ between groups.

To guard against the possibility that these results were attributable to an imbalance between the groups at baseline, a series of analyses of covariance were performed. For each efficacy outcome measure, parallel baseline measures were used as covariates (eg, for OSBD–R scores during reduction, OSBD–R scores during baseline were used as covariates). Because parental choice of location was used as a randomization stratum, this also was included in the model. None of the P values resulting from these analyses differed from those of the original t tests.

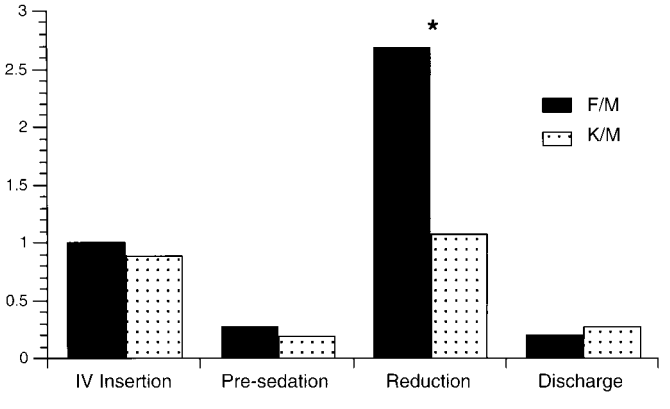

Fig 1. Effectiveness, OSBD–R scores. OSBD–R range, 0.0 to 23.5. Higher scores indicate greater distress (*$P \leq .0001$).

TABLE 2. Reduction Pain/Anxiety Scores

	Fentanyl/ Midazolam (n = 130)	Ketamine/ Midazolam (n = 130)	P Value
Reduction			
OSBD–R[a,b]	2.70 ± 2.16	1.08 ± 1.12	.0001
Pain[b,c]	5.55 ± 3.33	4.21 ± 3.30	.004
Anxiety[b,c]	5.49 ± 3.26	4.48 ± 3.26	.02

[a] OSBD–R scores range from 0.0 to 23.5; higher scores indicate greater distress.[38]
[b] Mean ± SD.
[c] Assessed by parents, 10-point visual analog scale; higher scores indicate greater anxiety or pain.

These models were then augmented by including the baseline FAS and parental expectation of the subjects' pain because each of these variables appeared to favor the K/M group at baseline. Again, there were only trivial changes in the P values.

Reduction was accomplished in all but one K/M subject and 3 F/M subjects. Deep sedation occurred in 87% of F/M and 89% of K/M subjects. No subject reached general anesthesia. Complete amnesia for the procedure occurred in 85% of F/M and 87% of K/M subjects (Table 3). Orthopedic surgeons favored K/M ($P \leq .0001$) (Table 3). Three F/M subjects received ketamine for successful reduction and 1 K/M subject required general anesthesia. Nine F/M and 10 K/M subjects had intraoperative pinning for fracture stabilization. Time for induction of sedation was equivalent between groups, but recovery was shorter for the F/M group (Table 3).

Mean first reduction dose for fentanyl was 1.58±.66 μg/kg and for ketamine was 1.05 ± .52 mg/kg. Mean total dose administered for all reduction attempts of fentanyl was 1.97 ± .85 μg/kg and for ketamine was 1.76 ± .73 mg/kg. Before first reduction attempts, more midazolam was administered to F/M than to K/M subjects (.15 ± .07 vs .11 ± .06 mg/kg; P = .0001). More midazolam also was administered to F/M than to K/M subjects in total dose (.17 ± .08 vs .13 ± .07 mg/kg; P = .0001).

Safety

F/M subjects experienced more hypoxia (P = .001) and received more breathing cues (P = .001) and supplemental oxygen (P = .04) than did K/M subjects (Fig 2). Two F/M subjects received naloxone (Fig 2) and supplemental oxygen, but neither subject was noted to be hypoxic nor received bag-valve-mask (BVM)-positive pressure ventilation. Two K/M subjects required brief BVM ventilations. One had laryngospasm and received nebulized racemic epinephrine and intravenous lidocaine. The stridor and respiratory distress resolved within 1 hour of administration of ketamine, and no additional problems occurred. The second subject received 3 BVM ventilations when his oxygen saturation decreased to 76%. Improved oxygenation occurred after airway maneuvers and oxygen supplementation, and no additional support was needed.

Post hoc analyses of respiratory complications were performed, controlling for midazolam dose (Fig 3). Respiratory complications occurred more frequently in F/M compared with K/M subjects, both among those who received low-dose midazolam (<.125 mg/kg) and those who received high-dose midazolam (≥.125 mg/kg). Respiratory complications occurred equally between high- and low-dose midazolam subgroups within F/M or K/M groups (Fig 3). Similar analyses controlling for fentanyl dose (high dose ≥1.25 μg/kg) or ketamine dose (high dose ≥1.25 mg/kg) also found that respiratory complications occurred no more frequently with high compared with low doses of fentanyl or ketamine.

During sedation and recovery, vomiting occurred more often in K/M than in F/M subjects (P = .03); most vomiting occurred during recovery (Table 4). No clinically apparent aspiration occurred. Mean time between last oral intake and sedation for subjects who vomited was 4.4 ± 2.5 hours, compared with 5.0 ± 2.4 hours for those who did not (P = .40). There were no differences between F/M and K/M subjects during these periods in frequency of emergence delirium, laryngospasm, or other adverse reactions (Table 4).

During the week after reduction, vomiting occurred more frequently in K/M subjects (P = .03) and crying in F/M subjects (P = .03). Although other minor adverse effects were common, there were no other differences in the prevalence of adverse effects

TABLE 3. Efficacy Measures of Medication Regimens

	Fentanyl/Midazolam	Ketamine/Midazolam	P Value
Reductions			
Successful (%)	127/130 (98)	129/130 (99)	.62
Single attempt (%)	99/125 (79)	98/125 (78)	.76
Number of attempts	1.21 ± .47	1.26 ± .53	.43
Sedation			
Deep (%)[a]	110/127 (87)	114/128 (89)	.55
Complete amnesia (%)[b]	104/122 (85)	109/126 (87)	.85
Orthopedists' satisfaction[c,d]	8.71 ± 2.21	9.61 ± .78	.0001
Procedure times (min)[e]			
Induction[d]	13.4 ± 9.1	13.1 ± 13.5	.82
Recovery[d]	113.7 ± 36.9	127.6 ± 56.2	.02

[a] Subject's deepest level of sedation during reduction as determined by direct observation. Levels included conscious (alert or purposefully responsive to verbal stimuli), deep (responsive to painful stimuli only), and general anesthesia (unresponsive to painful stimuli).[36]
[b] At discharge, subjects memory of reduction pain and events.
[c] 10-Point visual analog scale; higher scores indicate greater satisfaction.
[d] Mean ± SD.
[e] Induction indicates minutes between first midazolam dose and first orthopedic manipulation; recovery, minutes between first midazolam dose and discharge.

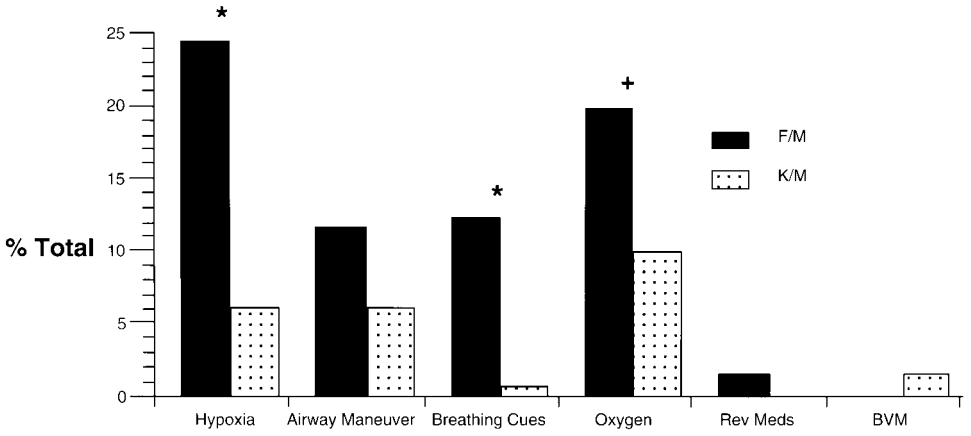

Fig 2. Safety, respiratory complications and interventions. Hypoxia indicates oxygen saturation < 90% while breathing room air; airway maneuver includes head tilt, chin lift, jaw thrust; breathing cues are verbal commands to breathe; oxygen indicates supplemental oxygen using nasal cannulae, mask, or BVM; reversal meds is naloxone. BVM indicates positive pressure ventilation using BVM device (*P = .001; +P = .04).

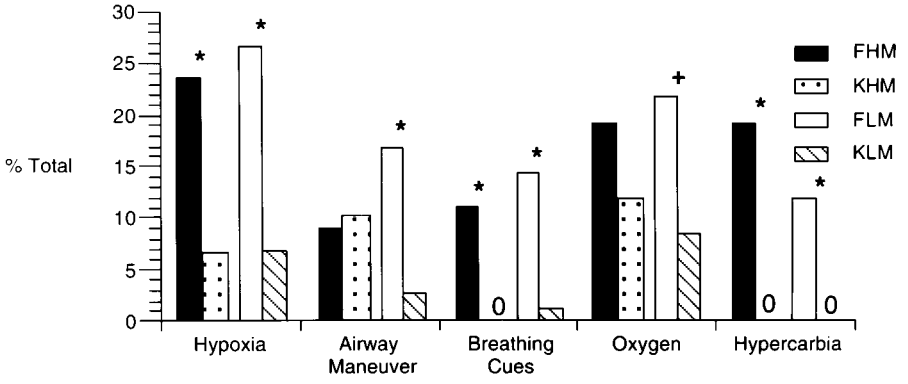

Fig 3. Respiratory complications: controlling for midazolam dose. FHM indicates fentanyl with high-dose midazolam (Midazolam dose [M] ≥ .125 mg/kg), n = 88; FLM, fentanyl with low-dose midazolam (M < .125 mg/kg), n = 41; KHM, ketamine with high-dose midazolam (M ≥ .125 mg/kg), n = 58; KLM, ketamine with low-dose midazolam (M < .125 mg/kg), n = 69 (*P ≤ .01; +P = .05).

during the first 24 hours or at 1 week after the procedure (Table 4).

DISCUSSION

Efficacy

During outpatient emergency orthopedic procedures, subjects who received K/M had less distress compared with subjects who received F/M. Both groups had high rates of successful fracture reduction and amnesia. Mean time for induction of sedation was the same for both groups, but mean time for recovery was shorter for the F/M group.

Health care providers and, consequently, subjects' families were not blinded to the study drug. This was to ensure subject safety and because the clinical effects of fentanyl and ketamine are distinguishable. However, OSBD–R scorers of the videotapes were blind to study purpose and design. Convergence of objective OSBD–R scores and parental ratings of their child's pain and anxiety during reduction supports the validity of the measured difference in distress between treatment regimens.

Despite a difference between groups in the children's assessment of their own distress before sedation, the F/M and K/M groups were equivalent in parental ratings of subjects' usual level of anxiety and ability to handle pain and in OSBD–R scores during iv insertion and presedation. Furthermore, the analyses of covariance, which used presedation variables as covariates (including FAS), did not alter the results. Thus, a randomization failure is an unlikely explanation for the K/M versus F/M differences observed during reduction.

These findings are consistent with those of Marx,[25] who found less distress during oncologic procedures in 22 children sedated with K/M compared with those sedated with meperidine/midazolam. Others[21–26] also have found that most children undergoing minor outpatient procedures did not require restraint when sedated with ketamine. Facilitation of completion of procedures with F/M[18] and the occurrence of amnesia with F/M[28,29] and K/M[25] also have been demonstrated previously. Although the time for induction of sedation in the present study was similar to that in others,[25,26] the longer time to discharge may be explained by a greater mean dose of midazolam and strict adherence to recommended discharge guidelines.[36,39]

Safety

Subjects who received F/M had more respiratory depression than those who received K/M. Both F/M and K/M protocols resulted in deep sedation in most patients. K/M subjects had more vomiting but not more emergence delirium both during recovery and in the week after the procedure. More respiratory complications in F/M subjects may have occurred because they received a greater mean midazolam dose compared with K/M subjects. However, after controlling for midazolam dose, the differences in complications between F/M and K/M remained. These analyses suggest that within the dosage ranges

TABLE 4. Occurrence of Adverse Effects

	Fentanyl/Midazolam (n = 130)	Ketamine/Midazolam (n = 130)	P Value
During sedation and recovery (%)			
Vomiting			
During procedure	0	(1)	1.00
During recovery	3 (2)	11 (9)	.03
Other adverse reactions[a]			
All other	19 (16)	25 (23)	.21
Emergence[b]	3 (2)	7 (5)	.33
Stridor or laryngospasm	1 (1)	1 (1)	1.00
During 24 hours after procedure (%)			
Dry mouth	25 (22)	31 (26)	.53
Sleepy	24 (21)	22 (18)	.60
Pleasant dreams	22 (20)	15 (13)	.13
Crying	22 (19)	19 (16)	.51
Dizziness	20 (17)	20 (16)	.86
Balance	16 (15)	18 (17)	.67
Headache	16 (14)	15 (12)	.73
Nausea	12 (10)	19 (16)	.21
Nightmares	10 (9)	7 (6)	.39
Vomiting	7 (6)	15 (12)	.10
Hallucinations	2 (2)	5 (4)	.29
During 7 days after procedure (%)			
Dry mouth	10 (9)	6 (5)	.26
Sleepy	6 (5)	5 (5)	.70
Pleasant dreams	23 (21)	19 (16)	.34
Crying	18 (16)	8 (7)	.03
Dizziness	10 (9)	6 (5)	.26
Balance	5 (5)	4 (4)	.74
Headache	14 (12)	13 (11)	.75
Nausea	4 (4)	6 (5)	.56
Nightmares	10 (9)	6 (5)	.26
Vomiting	0 (0)	5 (4)	.03
Hallucinations	2 (2)	0 (0)	.15

[a] Each of the following occurred in ≤7% of subjects: pruritis, double vision, shivers/shaking, nausea, dizziness, tachycardia, rash, abdominal pain, and incontinence.
[b] Dysphoria, hallucinations, and other distressed behavior occurring during recovery from sedation.

studied, the frequency of respiratory complications is attributable more to the administration of fentanyl than to the dose of midazolam.

Lack of correlation between similar differences in midazolam doses and changes in tidal volume, respiratory rate, minute ventilation, end-tidal Co_2 or minimal oxygen saturation has been documented previously.[40,41] Less respiratory depression with K/M compared with meperidine/midazolam[25] and preservation of respiratory function during sedation with ketamine also have been demonstrated.[21–26,31,32,42] However, respiratory arrest after ketamine administration in a 2-year-old has been reported.[43]

Vomiting is a recognized adverse effect of sedation with ketamine[31,32] and fentanyl.[10,18] Vomiting during recovery, although more frequent in K/M subjects, occurred in both groups. Both sedators and recovery nurses were vigilant for this complication. Although protective airway reflexes may be spared with ketamine,[31,32] aspiration has been reported.[44,45] No clinically apparent aspiration occurred in the 260 subjects in this study. However, aspiration pneumonia during induction of general anesthesia has been estimated to occur at a frequency of ≤5/10 000.[46] Although our sample size does not allow for a precise determination of the frequency of aspiration, the upper 95% confidence limit for the observed aspiration frequency of 0 in our subjects is 2.2%.

Ketamine, once used extensively in children,[31,32] lost popularity because of the occurrence of emergence hallucinations and dysphoria in up to 30% to 50% of adults.[31,32] Although Marx[25] recently reported a frequency of 33% in 15 children sedated with ketamine and midazolam, emergence delirium previously has been reported to occur in <10% of children.[31,32,22–24,26,47,48] Concurrent use of midazolam[31,32] and psychological preparation of subjects[49] may have resulted in our 5% frequency of emergence delirium.

Ketamine sedation of young children without midazolam may result in more rapid recovery,[22,24] because benzodiazepines slow ketamine metabolism.[31] However, larger doses of ketamine than those used in our study may be required. Whether sedation with ketamine alone in this age group results in equivalent distress reduction, procedural amnesia, emergence delirium, and possibly less respiratory depression is unknown and warrants additional investigation.

Parental presence during procedures lessens parental anxiety[50–53] but reduces children's distress inconsistently.[52–54] Lack of parental-presence effect on subjects' procedural distress in this study is consistent with these reports, but sedative effects of both regimens may have overwhelmed any differences in observed behavior associated with parental presence.

Significance

This first comparison of a commonly recommended regimen (F/M) and an increasingly used

regimen (K/M) for induction of deep sedation to facilitate intensely painful orthopedic procedures clarifies the efficacy and safety profile of each regimen in the ED setting. Because most patients were not fasted and required deep sedation for pain control and respiratory complications were not predicted by the dose of midazolam, fentanyl, or ketamine, there was considerable risk of adverse events. We believe the lack of significant adverse outcomes was attributable to meticulous adherence to recommended patient monitoring guidelines including provision of an experienced sedator whose sole responsibility was to monitor cardiopulmonary status and to facilitate early lifesaving interventions.[36] Our study demonstrates that deep sedation can be performed safely in the emergency setting in selected patients with appropriate personnel and monitoring. Furthermore, despite the lack of a ketamine reversal agent, the increased vomiting, and the longer recovery time, the effectiveness of the K/M regimen, with its more manageable safety profile, should encourage more widespread provision of effective analgesia and sedation during painful pediatric ED procedures.

Because this study was conducted in an ED staffed by nurses and physicians experienced in the care of critically ill and injured children and because only 5- to 15-year-old subjects undergoing extremely painful orthopedic procedures were studied, caution in generalization of these results to other clinical settings, ages, and procedures is warranted.

CONCLUSIONS

We conclude that during emergency orthopedic FR, intravenous ketamine/midazolam is more effective than fentanyl/midazolam for relief of pain and anxiety in children. Respiratory complications occur less frequently with ketamine/midazolam than with fentanyl/midazolam, but respiratory support may be needed with either regimen.

Both regimens are effective in facilitating fracture reduction and both produce amnesia in nearly all children, but average time required for recovery is longer for ketamine/midazolam than for fentanyl/midazolam. Vomiting occurs more frequently with ketamine/midazolam than with fentanyl/midazolam and emergence reactions occur in small and statistically equivalent numbers with both regimens.

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UPPER CRUST REVOLUTIONARIES

During the past 15 years, the US health care system has undergone breathtaking changes. It is no exaggeration to call this process a revolution. Authority was wrested from physicians and hospitals and conferred on health maintenance organizations (HMOs) and other managed-care insurers. The revolutionaries are not the downtrodden—low-income and disabled patients or underpaid hospital and nursing home workers. The revolutionaries are America's multibillion-dollar fortune 500 companies. They set off the insurrection in the 1980s by inducing or requiring their employees to obtain health insurance from managed-care insurers, especially HMOs. Whether employers will allow power to remain in the hands of HMOs remains to be seen.

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