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Original Contributions

ORAL ANALGESIA BEFORE PEDIATRIC KETAMINE SEDATION IS NOT ASSOCIATED WITH AN INCREASED RISK OF EMESIS AND OTHER ADVERSE EVENTS

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□ **Abstract—The objective of this study was to determine the association between recent administration of oral analgesics and frequency of adverse events during ketamine sedation in pediatric patients undergoing fracture reduction in the emergency department (ED). This retrospective study was conducted in the ED of a large, urban pediatric teaching hospital. Subjects were patients aged ≤ 18 years seen between November 1, 2004 and October 31, 2005 who received ketamine sedation for fracture reduction. Patients with and without prior oral analgesia within 6 h of ED presentation were compared with respect to emesis and other post-sedation complications. Of 471 evaluable patients who underwent ketamine sedation, 201 received oral analgesia within 6 h. The groups with and without recent oral analgesia were similar in age, weight, and fasting duration for solid foods. Ketamine doses (in mg/kg) were slightly greater in the no prior oral analgesic group (1.40 mg/kg vs. 1.54 mg/kg, respectively, mean difference 0.15 [95% confidence interval (CI) −0.26 to −0.03]). Among patients receiving oral analgesia, 10 of 201(5%) experienced emesis, in contrast to 7 of 270 (2.6%) in the no oral analgesic group, (difference in proportions 2.4% [95% CI −1.1 to 6.5]). Total adverse events were comparable for groups receiving oral analgesia (5%) or no oral analgesia (5.6%, difference in proportions −0.6% [95% CI −4.7% to 3.9%]). No association was found between administration of oral analgesia before procedural sedation and anesthesia and the frequency of emesis or other adverse events.** © 2008 Elsevier Inc.

□ **Keywords—oral analgesia; procedural sedation; adverse events; ketamine; acetaminophen with codeine; ibuprofen**

INTRODUCTION

Various influential organizations representing different disciplines, including the American Academy of Pediatrics, the American Pain Society, the Emergency Medical Services for Children Program, and the American College of Emergency Physicians, have written statements encouraging improved treatment of pain (1–4). However, pain in children remains remarkably under-treated.

Pediatric emergency department (ED) patients receive inadequate or no analgesia for pain due to burns, fractures, or sickle-cell vaso-occlusive crises (5–8). Children are less likely than adults to receive analgesia for fracture pain (9). Furthermore, children < 24 months of age are less likely than older children to receive analgesia for fractures and burns (9–11).

An American Academy of Pediatrics committee statement recommends administration of pain medication in ED triage (2). However, clinicians may be concerned about the impact on fasting status. A common practice is to withhold oral medications from patients likely to undergo procedural sedation. A recently published emer-

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gency medicine text includes the recommendation that "oral analgesia should never be given until the need for immediate operative repair or conscious sedation is ruled out" (12). Many patients, therefore, may not receive adequate pain management while awaiting procedural sedation and analgesia (PSA).

Numerous publications have reported the safety and efficacy of various pediatric PSA regimens (13–20). None has studied the relationship between pre-PSA oral analgesia and the incidence of adverse events. Although fasting duration before PSA has no demonstrated association with the incidence of adverse effect, the impact of recent administration of oral analgesia on adverse PSA events has not been previously studied (18,19). We undertook this study to investigate the association between recent administration of oral analgesic agents and the incidence of adverse effects in children receiving ketamine PSA in the ED.

METHODS

Study Design

The hospital Institutional Review Board approved this retrospective study of patients receiving ketamine PSA for fracture reduction between November 1, 2004 and October 31, 2005.

The study was conducted in an urban tertiary care children's hospital ED with an annual census of approximately 55,000 visits per year. The ED has a written policy permitting triage administration of oral analgesics including acetaminophen, ibuprofen, or acetaminophen with codeine. Recent administration of oral analgesic was not considered a modifier of the fasting status for patients who subsequently underwent PSA. We currently use ketamine sedation without adjunctive benzodiazepines or anti-cholinergic agents in our pediatric ED for fracture reductions. We require fasting for 2 h after consumption of liquids and 4 h after solid foods. At our facility, recent administration of oral analgesics does not prolong the fasting required for PSA. Clinical nurses complete a standardized, hospital-wide sedation record for every episode of PSA.

We identified subjects by a search among patients treated in the ED from November 1, 2004 through October 31, 2005 using codes for "fracture" and "anesthesia" of the International Classification of Diseases, Ninth Edition, Clinical Modification. We included patients up to their 18th birthday who underwent PSA for closed reduction of upper or lower extremity fracture(s). We excluded patients due to: incomplete records, including lack of documentation of analgesic dose or time administered, and missing documentation regarding return to pre-sedation status and prior receipt of any medication with potential anti-emetic effect (most commonly promethazine before transfer). Two groups of patients were compared: those receiving oral analgesic agents before procedural sedation and analgesia and those not receiving an oral analgesic.

Clinical nursing staff completed a standardized, hospital-wide sedation record for every episode of PSA. This document as well as the remainder of the patient record for the ED visit was utilized to extract data.

Sample size was calculated based on the following information. The rate of emesis in patients undergoing ketamine (± midazolam) PSA shows a broad range. Based on data from our institution's observed experience demonstrating 3% frequency of emesis after ketamine sedation in the pediatric ED, a rate well within the broad range previously cited in the literature, a sample size was calculated (13,18–21). This generated a sample size of 198 per group to demonstrate therapeutic equivalence, with alpha set at 0.05 and beta at 0.10 (22,23).

Three of four investigators abstracted data from the ED triage sheet, ED physician notes, nursing notes, and sedation records. We collected demographic information (age, gender, weight), type and time of pre-PSA analgesic administration, time from last solid food and clear liquid intake, time to initiation of PSA, total dosage of ketamine, other parenteral analgesics, emesis and other adverse effects after PSA and interventions required were abstracted from the triage sheet, ED physician notes, nursing notes, and sedation record. We abstracted demographic information (age, gender, weight) from the remainder of the medical record. If discrepancies existed among different portions of the medical record, we used the fasting intervals on the sedation record. Time elapsed between oral analgesic and sedation was calculated based on the most recent administration of oral analgesic before PSA. Our division's research director and senior investigator reviewed the resulting database to verify accuracy on approximately 5% of charts and to screen for missing or improbable values (excessively large or negative values for time intervals).

Our primary outcome measurement was the intergroup difference in proportions experiencing emesis after ketamine sedation. Secondary outcome measure was the frequency of all other cardiorespiratory adverse events. Additional adverse events included: hypoxia (oxygen saturation requiring supplemental oxygen), hypoventilation, laryngospasm, apnea, bradycardia, or tachycardia.

We calculated a sample size of 198 per group to demonstrate equivalence between groups with α set at 0.05 and β at 0.10, based on our institution's observed experience of a 3% frequency of emesis after ketamine

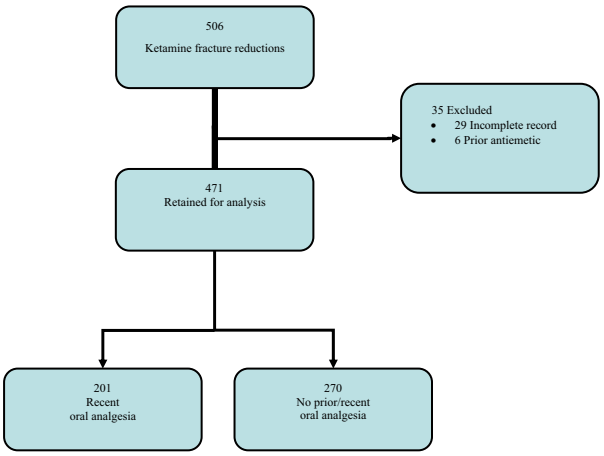

Figure 1. Study inclusion diagram.

sedation in the pediatric ED. Because no published data describe the effect of recent oral analgesics on sedation-related emesis, we chose 5% to represent a clinically significant difference in this adverse effect (22,24).

Statistical analysis was performed using SPSS version 11.5.0 (SPSS Inc., Chicago, IL). We compared the rates of emesis, fasting time durations, and patient demographics with and without prior oral analgesia by calculating 95% confidence intervals constructed around point estimates for differences in proportions by the method of Newcombe (23). We performed a secondary analysis comparing patients who received oral analgesics ≤ 4 h before PSA with all others who received no analgesics within 4 h of PSA.

RESULTS

There were 506 patients who received ketamine sedation for fracture reduction during the 12-month study period. We excluded 35 patients due to incomplete records (n = 29) and prior anti-emetic (n = 6, most commonly promethazine before interfacility transfer) (Figure 1). The remaining 471 patients were retained for analysis.

The main analysis compared the recent (≤ 6 h) oral analgesia group (n = 201) with the no oral analgesia group (n = 270). The two groups were similar with regard to age, weight, and fasting duration for solid foods (Table 1). The no oral analgesia group was predominantly male, received a higher weight-based dose of ketamine, had a longer fasting duration for liquids, and was more likely to receive intravenous analgesia (Table 1). Medications administered to the recent oral analgesia group included: acetaminophen with codeine (n = 146), ibuprofen (n = 31), acetaminophen (n = 11), and > 1 oral agent (n = 13). Emesis occurred in 10 of 201 (5%) of the recent oral analgesia group and in 7 of 270 (3%) of the no oral analgesia group. The total adverse events (15; 6%) of the no oral analgesia group consisted of emesis, hypoxia (6; 2%), hypoventilation (continuous positive airway pressure applied, 1; 0.4%) and tachycardia (1; 0.4%). All adverse events in the recent oral analgesia group consisted of emesis. No statistically significant difference existed in the rates of emesis or total adverse events.

The secondary analysis using the 4-h cutoff for recent oral analgesia group (Table 2) revealed emesis in 7 of 138 (5%) of the recent oral analgesia group and in 10 of 333 (3%) of the no oral analgesia group. The other cardiorespiratory adverse events occurred in the no oral analgesia group.

A total of 25 patients had adverse events (Table 3). Fifteen (60%) received intravenous analgesia, and 9 (36%) received both oral and intravenous analgesia before PSA. Seven (28%) received no analgesia. Eight of the 17 patients (47%) who experienced emesis received both intravenous and oral analgesia ≤ 6 h before PSA.

Table 1. Characteristics of Patients Undergoing Ketamine Sedation, Grouped According to Administration of Oral Analgesics within 6 Hours

Characteristic	Recent (≤ 6 h) Oral Analgesia (n = 201)	No Oral Analgesia (n = 270)	Difference (95% CI)
Age (years)	8.2 ± 3.6	8.5 ± 3.9	−0.3 (−1.0 to 0.4)
Gender (male)	124 (62%)	192 (71%)	−9% (−18% to −1%)
Weight (kg)	33.4 ± 17.2	34.2 ± 16.7	−0.8 (−3.9 to 2.3)
Ketamine dose (mg/kg)	1.4 ± 0.5	1.5 ± 0.7	−0.15 (−0.26 to −0.03)
Time from oral analgesic to ketamine (h:min)	3:22 ± 1:11	—	—
Fasting duration, solids (h:min)	8:10 ± 3:41	8:48 ± 3:58	−0:38 (−1:21 to 0:04)
Fasting duration, liquids (h:min)	6:59 ± 3:05	7:59 ± 3:33	−1:00 (−1:37 to −0:23)
i.v. Analgesia before sedation	75 (37%)	137 (51%)	−13% (−22% to −4%)
Emesis	10 (5%)	7 (3%)	2% (−1% to 7%)
All complications	10 (5%)	15 (5.6%)	−0.6% (−4.7% to 3.9%)

CI = confidence interval.
Data presented as mean ± SD or number (%).

Table 2. Characteristics of Patients Undergoing Ketamine Sedation, Grouped According to Administration of Oral Analgesics within 4 Hours

Characteristic	Recent (≤ 4 h) Oral Analgesia (n = 138)	No Oral Analgesia (n = 333)	Difference (95% CI)
Age (years)	8.0 ± 3.5	8.5 ± 3.9	−0.5 (−1.2 to 0.3)
Gender (male)	85 (62%)	231 (69%)	−8% (−17% to 2%)
Weight (kg)	31.5 ± 16.8	34.8 ± 16.9	−3.3 (−6.7 to 0.02)
Ketamine dose (mg/kg)	1.4 ± 0.5	1.5 ± 0.7	−0.14 (−0.27 to −0.02)
Time from oral analgesic to ketamine (hr:min)	2:44 ± 0:48	—	—
Fasting duration, solids (hr:min)	7:43 ± 3:36	8:52 ± 3:55	−1:09 (−1:55 to −0:23)
Fasting duration, liquids (hr:min)	6:37 ± 3:05	7:57 ± 3:26	−1:20 (−2:00 to −0:40)
i.v. Analgesia before sedation	50 (36%)	161 (48%)	−12% (−21% to −2%)
Emesis	7 (5.1%)	10 (3%)	2% (−2% to 7%)
All complications	7 (5.1%)	18 (5.4%)	−0.3% (−4.3% to 5.1%)

CI = confidence interval.
Data presented as mean ± SD or number (%).

DISCUSSION

The incidence of emesis in our study associated with ketamine sedation for fracture reduction was low (3–5%) but consistent with previously reported ranges (13,18–21).

The use of oral analgesia before PSA does not result in a statistically significant difference in the frequency of emesis or a statistically significant difference in the overall frequency of adverse events. Closer examination reveals that the difference in frequency of emesis between the recent oral analgesia and no analgesia groups is small

Table 3. All Adverse Events in Patients Receiving Ketamine Sedation

Age (Years)	ASA Physical Status	Gender	Prior Oral Analgesic	Time between POA and Ketamine (h:min)	Prior Parenteral Agent(s)	Time between IVA and Ketamine (h:min)*	Fasting Duration (h:min)†	Ketamine Dose (mg/kg)	Complication
12.1	1	Male	None		None		9:20	1.72	Emesis
6.8	1	Female	None		None		8:25	1.09	Emesis
13.9	1	Male	None		Morphine sulfate	0:50	11:10 (5:10)	0.98	Emesis
13.9	1	Male	None		Morphine sulfate	1:25	7:15	1.00	Emesis
12.8	1	Male	None		None		21:55	0.72	Emesis
14.7	1	Male	None		Morphine sulfate	0:35	6:00	1.47	Emesis
12.1	1	Male	Acetaminophen-codeine	8:40	None		8:40	1.00	Emesis
9.9	1	Male	Acetaminophen-codeine	4:58	Morphine sulfate	0:22	7:07	1.55	Emesis
11.7	1	Male	Acetaminophen-codeine	3:01	Morphine sulfate	2:31	5:06	1.08	Emesis
14.1	1	Male	Acetaminophen-codeine	1:04	Morphine sulfate	0:20	6:20 (1:20)	0.85	Emesis
8.2	1	Male	Acetaminophen-codeine	3:03	Morphine sulfate	2:08	4:33 (3:33)	2.10	Emesis
10.9	1	Female	Ibuprofen	4:30	None		7:45	1.04	Emesis
13.2	2	Male	Acetaminophen-codeine	3:30	Morphine sulfate	1:10	9:00	1.00	Emesis
7.9	1	Male	Acetaminophen-codeine	3:49	None		8:49	2.47	Emesis
13.4	1	Male	Acetaminophen-codeine	3:58	Morphine sulfate	0:13	18:58 (4:48)	1.03	Emesis
12.8	1	Male	Acetaminophen-codeine	4:43	Morphine sulfate	3:19	8:44	1.01	Emesis
13.2	1	Male	Acetaminophen-codeine	0:59	Fentanyl	0:09	4:24	1.12	Emesis
1.7	1	Male	None		None		8:50	4.00	Hypoxia
17.2	1	Male	None		Morphine sulfate	0:45	5:40	2.75	Hypoxia
6.9	1	Male	None		Morphine sulfate	−1:05	6:25	1.39	Hypoxia
8.5	1	Male	None		None		14:30	1.24	Tachycardia
4.8	1	Male	None		Morphine sulfate, midazolam	−0:40	4:45	1.60	Hypoventilation
9.7	1	Male	None		None		12:25	2.91	Hypoxia
10.5	1	Female	None		None		6:50	1.52	Hypoxia
14.4	1	Male	Acetaminophen-codeine	6:45	Morphine sulfate	1:05	9:35	1.06	Hypoxia

* Negative values indicate administration *after* the ketamine.
† For fasting durations < 6 h, data in parentheses represent fasting times for clear liquids, if different from fasting times for solid food.
ASA = American Society of Anesthesiologists; POA = oral analgesia; IVA = intravenous analgesia.

but not zero. The lower limit of the 95% confidence interval encompasses a zero difference, but the upper limit exceeds the a priori definition for clinically significant difference in rates. Taken together, our findings suggest that the decision between early oral or parenteral analgesia entails a balance between two types of adverse effects, which should not have serious clinical consequence in the well-monitored patient—a potential increase in emesis with oral analgesia and a greater frequency of hypoxia and hypoventilation with parenteral analgesia.

Our findings are consistent with studies by Roback et al. and Agrawal et al. that demonstrate no association between pre-procedural fasting and the incidence of adverse events (18,19).

Prior studies have credited midazolam with the decreased rate of emesis when used in conjunction with ketamine (20). Although we omit anti-cholinergic and benzodiazepine adjuncts in our routine PSAs, we report a frequency of emesis at the low end of these previously reported rates.

Our findings, together with those of Roback et al. and Agrawal et al., suggest that the consensus-based American Society of Anesthesiologists fasting guidelines may not rigidly apply to PSA in the pediatric ED (25,26).

Prior studies address the prescribing practices for children vs. adults, for subtype of pain etiology, and in variable prescribing settings. Gender subtyping in the preceding groupings was not specified. Future studies should evaluate the effect of oral analgesia on pain score reduction and the relationship to concurrent use of intravenous analgesia, weight-based ketamine dose, and adverse events.

LIMITATIONS

The limitations of this study include its dependence on the accuracy and completeness of the medical record for chronologic data and adverse events. ED clinicians may have inaccurately recorded chronologic data or incompletely described adverse events. Chronologic data also are subject to inaccuracy in the calibration of timepieces used in clinical settings and in the documentation of time intervals by clinical personnel (27,28).

Clinicians may have failed to observe minor transient adverse events or may have observed and disregarded or neglected to document them.

The investigators reviewing charts were blinded to neither the study objectives nor the outcomes. However, strict study definitions were created in an attempt to minimize bias.

We were unable to study the interaction of recent oral analgesic administration with many other potential risk factors for adverse events, such as composition of the analgesic (liquid vs. tablet), fasting status, and composition and quantity of last meal.

CONCLUSIONS

This study supports the hypothesis that recent oral analgesia does not impact the incidence of adverse events in patients undergoing ketamine procedural sedation and analgesia. Emergency medicine providers and other primary care providers should consider oral analgesia early in the patient encounter, regardless of the anticipated need for PSA.

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