Randomized Clinical Trial of Propofol Versus Ketamine for Procedural Sedation in the Emergency Department

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Abstract

Objectives: The objective was to compare the occurrence of respiratory depression, adverse events, and recovery duration of propofol versus ketamine for use in procedural sedation in the emergency department (ED).

Methods: This was a randomized nonblinded prospective clinical trial of adult patients undergoing procedural sedation for painful procedures in the ED. Patients with pain before the procedure were treated with intravenous (IV) morphine sulfate until their pain was adequately treated at least 20 minutes before starting the procedure. Patients were randomized to receive either propofol 1 mg/kg IV followed by 0.5 mg/kg every 3 minutes as needed or ketamine 1.0 mg/kg IV followed by 0.5 mg/kg every 3 minutes as needed. Doses, vital signs, nasal end-tidal CO_2 ($ETCO_2$), and pulse oximetry were recorded. Subclinical respiratory depression was defined as a change in $ETCO_2$ of >10 mm Hg, an oxygen saturation of <92% at any time, or an absent $ETCO_2$ waveform at any time. Clinical interventions related to respiratory depression were noted during the procedure, including the addition of or increase in the flow rate of supplemental oxygen, the use of a bag-valve mask apparatus, airway repositioning, or stimulation to induce breathing. After the procedure, patients were asked if they experienced pain during the procedure and had recall of the procedure. Physicians were asked to describe any adverse events or the occurrence of recovery agitation.

Results: One-hundred patients were enrolled; 97 underwent sedation and were included in the analysis. Fifty patients received propofol and 47 received ketamine. Subclinical respiratory depression was seen in 20 of 50 patients in the propofol group and 30 of 47 patients in the ketamine group (p = 0.019, effect size 22.8%; 95% CI = 4.0% to 43.6%). Clinical interventions related to respiratory depression were used in 26 of 50 propofol patients and 19 of 47 ketamine patients (p = 0.253, effect size = −13.7%; 95% CI = −33.8% to 6.4%). The median times of the procedures were 11 minutes (range = 4 to 33 minutes) for the ketamine group versus 10 minutes (range = 5 to 33 minutes) for the propofol group (p = 0.256). The median time to return to baseline mental status after the procedure was completed was 14 minutes (range = 2 to 47 minutes) for the ketamine group and 5 minutes (range = 1 to 32 minutes) for the propofol group (p < 0.001). Pain during the procedure was reported by 3 of 50 patients in the propofol group and 1 of 47 patients in the ketamine group (effect size = −3.9%, 95% confidence interval [CI] = −11.9 to 4.1). Recall of some part of the procedure was reported by 4 of 50 patients in the propofol group and 6 of 47 patients in the ketamine group (effect size = 4.8%, 95% CI = −7.6% to 17.1%). Forty-eight of 50 procedures were successful in the propofol group and 43 of 47 in the ketamine group (p = 0.357, effect size = 0.3%; 95% CI = −7.8% to 8.4%). Recovery agitation was reported in 4 of 50 in the propofol group and 17 of 47 in the ketamine group (effect size = 28.2%, 95% CI = 12.4% to 43.9%).

Conclusions: This study detected a higher rate of subclinical respiratory depression in patients in the ketamine group than the propofol group. There was no difference in the rate of clinical interventions related to respiratory depression, pain, or recall of the procedure between the groups. Recovery agitation was seen more frequently in patients receiving ketamine than in those receiving propofol. The time to regain baseline mental status was longer in the ketamine group than the propofol group. This study suggests that the use of either ketamine or propofol is safe and effective for procedural sedation in the ED.

ACADEMIC EMERGENCY MEDICINE 2010; 17:604–611 © 2010 by the Society for Academic Emergency Medicine

Keywords: procedural sedation, emergency department, propofol, ketamine

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Received October 9, 2009; revisions received December 16 and December 23, 2009; accepted December 24, 2009.
This work was presented at the Society for Academic Emergency Medicine annual meeting, Chicago, IL, May 2007.
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ISSN 1069-6563
PII ISSN 1069-6563583

doi: 10.1111/j.1553-2712.2010.00776.x

Patients in the emergency department (ED) undergoing painful procedures, such as orthopedic manipulations or abscess drainage, often require sedation to successfully perform the procedure. This is achieved with the use of sedative agents such as propofol, administered at doses that allow patients to maintain airway reflexes and have some response to verbal stimuli (moderate sedation) or to pain (deep sedation). Propofol has been well studied for this purpose and provides adequate sedation to perform procedures successfully with a minimum of cardiorespiratory side effects and a short duration of action.[1–6] Propofol can be used to induce both moderate and deep sedation.[7,8] The rate of adverse effects for propofol sedation in the ED has been reported to be 5%, with hypoxia present in 5%–30% of reports.[5]

It is generally accepted that propofol has sedative and amnestic properties and lacks any specific analgesic effect. The clinical significance of procedural pain that a patient experiences, but cannot later recall, remains unclear.[9,10] Amnesia from propofol lasts an average of 15.7 minutes in adults who have received 1 mg/kg propofol, followed by 0.5 mg/kg until sedated.[11] Patients receiving these doses of propofol often demonstrate a response to noxious stimuli during the procedure that they do not later recall; such a response is the defining characteristic of deep sedation relative to general anesthesia for nondissociative agents.

Ketamine hydrochloride is also used for sedation in the ED, although it has been studied more extensively in children than in adults.[12–19] It is a phencyclidine derivative that causes dissociation between the cortical and limbic systems, preventing the patient from perceiving sensory stimuli. It has a rapid onset and short duration of action and produces procedural amnesia and analgesia. It has not been associated with high rates of respiratory compromise[13,16,17,19,20] and is generally thought to be a respiratory stimulant, although some respiratory depression can occur immediately after it is given in an intravenous (IV) bolus.[13,16,17,19,20] It has been associated with respiratory compromise in 6% of adult patients undergoing moderate sedation,[16] with lower rates reported in children.[12,15,19] Ketamine has been associated with recovery agitation, which can range from episodes of agitation or delirium, to severe reactions associated with hallucinations, concerns about which have limited its use in adults. This has been reported to occur to some extent in 5% to 25% of patients.[13,16–18]

This study prospectively compared procedural sedation using propofol to procedural sedation using ketamine in adults. The primary objective was to compare the rate of subclinical respiratory depression and the rate of clinical interventions related to respiratory depression. Secondary outcomes included the level of sedation achieved, the rate of adverse events, the time required for patients to return to baseline mental status after the procedure, the success of the procedure, and the patient-derived outcome factors of perceived pain, recall of the procedure, and satisfaction with the care received.

METHODS

Study Design

This was a prospective, randomized, nonblinded clinical trial of propofol versus ketamine for procedural sedation of patients undergoing painful procedures between January 1, 2007, and March 1, 2009. The Institutional Review Board of Hennepin County Medical Center approved the study. Patients provided prospective informed consent prior to enrollment.

Study Setting and Population

Hennepin County Medical Center is an urban medical center with approximately 99,000 ED patient visits per year. In our ED, procedural sedation with propofol is performed at the discretion of the treating emergency physician.

All adult (age ≥ 18 years) ED patients who were to receive moderate procedural sedation using propofol were eligible for study enrollment. This study was performed concurrently with a study of patients undergoing deep procedural sedation using propofol with and without alfentanil.[10] Patients were excluded if they were unable to give consent, had an American Society of Anesthesiologists (ASA) Physical Assessment Score of >2,[21] had a known hypersensitivity to either study medication, were pregnant, or had clinical evidence of intoxication prior to the start of the procedure. Patients were not eligible for this study if the treating physician planned to use deep procedural sedation rather than moderate sedation.

Study Protocol

Patients with pain prior to procedural sedation were treated with IV morphine (0.1 mg/kg IV followed by 0.05 mg/kg IV q 10 minutes as needed/tolerated for pain relief) as soon as possible in their treatment and at least 20 minutes prior to their sedation procedure. Patients were placed on cardiac, blood pressure, pulse oximeter, and nasal sample end-tidal CO_2 ($ETCO_2$) monitors, as per standard guidelines for procedural sedation in our ED. The $ETCO_2$ monitor (Capnocheck Plus, Smiths Medical, BCI, Dublin, OH) displays a continuous numerical $ETCO_2$ value and waveform. Baseline values were recorded. Patients were then randomized to receive either propofol 1 mg/kg bolus followed by 0.5 mg/kg every 3 minutes as needed for sedation or ketamine 1.0 mg/kg IV followed by 0.5 mg/kg every 3 minutes as needed for sedation. Randomization was achieved by selecting a sequentially numbered sealed envelope containing the group assignment, which had been determined using a computer-generated list of random numbers. Neither patients nor physicians were blinded to the agent being administered. The use of supplemental oxygen during procedural sedation was at the discretion of the treating physician. Patients did not receive pain medications other than the study drugs within 20 minutes of the start of the procedure.

Data were collected by a designated trained research assistant (available 24 hours a day) during the procedure and then entered into an Excel (Microsoft Corp., Redmond, WA) spreadsheet. $ETCO_2$ was recorded

continuously throughout the procedure. Pulse oximetry, heart rate, blood pressure, and respiratory rate were monitored continuously. The lowest value of each during every 1-minute period was manually recorded. The modified observer's assessment of alertness score (OAAS) was also recorded every minute. Any loss of $ETCO_2$ waveform or use of airway adjuncts, such as bag-valve mask assisted respirations or oral airway placement, was noted by the research assistant. Any clinical interventions related to respiratory depression were noted and recorded as well.

Measures

Subclinical respiratory depression was defined as a change from baseline $ETCO_2$ of >10 mm Hg, an oxygen saturation of <92% at any time during the procedure, or airway obstruction with cessation of gas exchange at any time (noted by an absent $ETCO_2$ waveform).[4,6,7,22–24] These are criteria we have used to detect subclinical respiratory depression in previous studies of procedural sedation. It is presumed that increases in $ETCO_2$ are indicative of hypercapnea and decreases are due to increased mixing of the breath sample with room air due to airway obstruction and/or decreasing tidal volume.

In addition to these objective measures, clinical interventions related to respiratory depression were detected by specific queries to the physician performing the procedure after its completion, including any addition of or increase in the flow rate of supplemental oxygen, the use of a bag-valve mask apparatus to increase ventilation, repositioning of the patient's airway to improve ventilation, or stimulation of the patient to induce breathing.[10,25] After the procedure, the physician was asked to complete a standardized data collection sheet to note any adverse events experienced by the patients, including, but not limited to, vomiting or aspiration, intubation, transfers to a higher level of care after the procedure, hypotension (defined as a systolic blood pressure [sBP] < 100 mmHg), or arrhythmias. The occurrence of recovery agitation was measured by specific query to the treating physician on the data collection sheet. Physicians were asked to note any behaviors after the procedure that could be considered recovery agitation, including anxiety, euphoria, agitation, confusion, or hallucinations that either led to a specific treatment or demonstrated substantial severity.[18]

The depth of sedation was measured using a subjective scale, the modified OAAS.[26] This is a five-point scale describing the patient's clinical appearance of sedation.

After the patients returned to their baseline mental status, they were asked if they felt any pain during the procedure or were able to recall any of the procedure (yes/no). They were also asked if they were satisfied with the treatment they received during the procedure.[4,6,22]

Data Analysis

Data were analyzed using STATA 10.0 (StataCorp, College Station, TX). The proportion of patients with subclinical respiratory depression, pain, recall, and clinical interventions related to respiratory depression were compared, using chi-square tests and 95% confidence intervals (CIs). The time to return of baseline mental status and the OAAS scores were described using median and interquartile ranges and were tested for equality between the two groups using Wilcoxon rank sum tests.

There is no previous work using these methods of measuring respiratory depression in patients receiving ketamine that we are aware of upon which to base the size of our study. Assuming a baseline incidence of subclinical respiratory depression of 30% from previous work done with propofol,[4,6] to detect a 25% difference in the proportion of patients with subclinical respiratory depression between the two groups, with an alpha of 0.05 and a beta of 0.2 (80% power), power analysis indicated that 50 patients per group were required.

RESULTS

Demographics

One-hundred patients were enrolled in the study; 97 underwent sedation and were included in the analysis. Fifty patients received propofol and 47 received ketamine. Three patients who had been assigned to ketamine did not subsequently undergo procedural sedation due to changes in their clinical need for the procedure. Patient enrollment is shown in Figure 1. Twenty-six eligible patients who presented to the ED during the study period underwent sedation before they were approached for enrollment in the study. Nineteen patients refused to participate in the study after being approached. The characteristics of the study subjects are presented in Table 1, and the procedures for which patients were sedated are described and presented in Table 2.

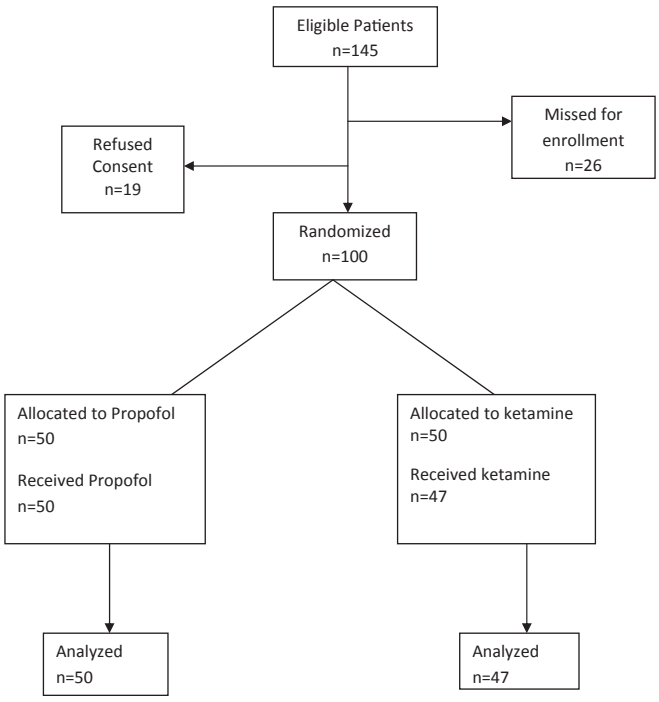

Figure 1. Patient enrollment.

Table 1
Characteristics of the Study Subjects

	Ketamine (n = 47)	Propofol (n = 50)	Difference (95% CI)
Median age, yr (range)	30 (18–73)	34.5 (18–85)	−2.3 (−8.2 to 3.5)
Male (%)	25 (53.2)	24 (48.0)	5.0 (−11.2 to 21.3)
Weight (kg), median (range)	82 (55–158)	72 (50–141)	12.7 (3.8 to 21.6)
ASA Physical Status Score = 1 (%)	29 (61.7)	31 (62.0)	0.7 (−12.5 to 13.4)
Initial sBP (mm Hg), median (range) IQR	127.5 (83–187) 123–145	131.5 (84–201) 122–140.5	−1.2 (−9.3 to 7.0)
Initial $ETCO_2$ (mm Hg), median (range) IQR	37 (34–44) 34–44	39 (21–52) 35–42	−0.89 (−3.63 to 1.85)
Initial oxygen saturation, median (range) IQR	100 (96–100) 98–100	100 (94–100) 99–100	−0.18 (−0.79 to 0.43)
Received supplemental oxygen before the procedure, % (n/N) 95% CI	53.2 (25/47) 38.1–67.9	86.0 (43/50) 73.3–94.2	−32.8 (−50.2 to −15.4)
Initial OAAS, median (range) IQR	5 (3–5) 5–5	5 (4–5) 4–5	−0.21 (−0.5 to 0.35)
Initial heart rate (beats/min), median (range) IQR	88 (59–121) 76–103	84 (43–147) 74–101	0.68 (−7.5 to 8.6)
Received morphine >30 min before procedure, n/N (%)	34/47 (72.3)	36/50 (72.0)	0.3 (−17.9 to 18.6)
Median morphine dose, mg/kg (range, mg)	0.1 (0.02–0.25)	0.1 (0.02–0.21)	−0.04 (−0.11 to 0.04)

ASA = American Society of Anesthesiologists; $ETCO_2$ = end-tidal CO_2; IQR = interquartile range; OAAS = modified observer's assessment of alertness score; sBP = systolic blood pressure.

Table 2
Procedures Performed

Procedure	Ketamine, n (%)	Propofol, n (%)	% Difference (95% CI)
N	47	50	
Incision and drainage of abscess	21 (44.7)	19 (38.0)	−6.7 (−26.2 to 12.9)
Fracture reduction	12 (25.5)	15 (30.0)	4.5 (−13.3 to 22.3)
Dislocation reduction	13 (27.7)	12 (24.0)	−3.7 (−21.1 to 13.7)
Tibial traction pin placement	1 (2.1)	1 (2.0)	−0.1 (−5.7 to 5.5)
Cardioversion	0 (0)	1 (2.0)	2.0 (−1.9 to 5.9)
Chest tube placement	0 (0)	1 (2.0)	2.0 (−1.9 to 5.9)

Drug Dosing, Procedure Time, and Success

The main results are described in Table 3. Procedural success was achieved in 45 of 47 (95.7%) of the ketamine group and 48 of 50 (96%) in the propofol group (difference = 0.3%, 95% CI = −8.3% to 7.7%). The unsuccessful procedures included two dislocation reductions, one in each group, and two abscess incision and drainage procedures, also with one in each group.

Respiratory Depression

The rate of subclinical respiratory depression was 63.8% in the ketamine group and 40.0% in the propofol group (difference = 23.8%, 95% CI = 4.5% to 43.1%, p = 0.02). There was no difference in the individual parameters of subclinical respiratory depression between the groups. Clinical interventions related to respiratory depression were present in 26 of 50 propofol patients and 19 of 47 ketamine patients (p = 0.253, effect size = −13.7%, 95% CI = −33.8% to 6.4%). Clinical interventions related to respiratory depression are described in Table 4.

Adverse Events

No serious adverse events were detected during the study. Recovery agitation was reported in 17 (36.2%) patients in the ketamine group and four (8.0%) patients in the propofol group (difference 28.2%, 95% CI = 12.4% to 43.9%). Four patients in the ketamine group required treatment with IV midazolam for recovery agitation. The other patients did not require additional medications for recovery agitation. All of these episodes resolved without further incident.

Five patients had a sBP less than 100 mm Hg at some time during the procedure; two received propofol and three received ketamine. The lowest sBP recorded in the study was 79 mm Hg for the ketamine group and 73 mm Hg for the propofol group. All of these subjects had recovery of normal blood pressure with IV fluids within 2 minutes; none were noted to have negative sequelae from this. No cardiac rhythm abnormalities, episodes of vomiting or aspiration, intubation, transfers to a higher level of care after the procedure, or arrhythmias were noted during any of the procedures.

DISCUSSION

We detected a higher rate of subclinical respiratory depression in patients sedated with ketamine than in patients sedated with propofol, but found similar rates

Table 3
Main Results for the Procedures

Procedure	Ketamine (n = 47)	Propofol (n = 50)	Difference (95% CI)
Initial sedative bolus (mg/kg), median (range) IQR	1.00 (0.67–1.83) 0.95–1.01	1.00 (0.30–1.50) 0.95–1.05	
No. of sedative doses, median (range) IQR	1 (1–4) 1–1	3 (1–7) 24	
Total sedative dose (mg/kg), median (range) IQR	1.00 (0.85–3.00) 1.00–1.07	1.46 (0.65 to 3.8) 1.13–2.50	
Subclinical respiratory depression, n/N (%) 95% CI	30/47 (63.8) 48.5 to 77.3	20/50 (40.0) 26.4 to 54.8	−23.8 (−43.1 to −4.5)
Maximum absolute change from baseline $ETCO_2$ (mm Hg), median (range) IQR	10 (5–15) 0–34	8.5 (6–19) 0–42	−0.9 (−4.5 to 2.7)
Lowest oxygen saturation during procedure, median (range) IQR	96.5 (67–100) 92–99	99.0 (45–100) 94–100	−0.69 (−3.9 to 2.5)
Heart rate maximum (beats/min), median (range) IQR	119 (79–180) 101–130	96 (57–147) 85–109	18.4 (10.3 to 25.5)
Change in $ETCO_2$ >10 mm Hg, n/N (%) 95% CI	21/47 (44.7) 29.9 to 59.4	15/50 (30.0) 16.8 to 43.2	14.7% (−4.8 to 34.1)
Capnogram waveform absent at any time (%) 95% CI	11/47 (23.4) 10.8 to 36.0	9/50 (18.0) 7.0 to 29.0	5.4% (−11.0 to 21.9)
Oxygen saturation <92% at any time, n/N (%) 95% CI	6/47 (12.7) 2.9 to 22.7	7/50 (14.0) 4.0 to 24.0	−1.2 (−15.1%to 12.6)
Lowest blood pressure recorded during procedure (mm Hg), median (range) IQR	126 (79–187) 118–139	120.5 (73–178) 110–130	8.3 (0.2 to 16.3)
% decrease in sBP from baseline (range) IQR	0.0 (0–37.8) 0–0	8.5 (0–26.1) 3.5–12.9	−6.4 (−9.2 to −3.5)
OAAS score, median (range) IQR	2 (1–4) 1–3	2 (1–5) 1–3	−0.15 (−0.49 to 0.20)
Total time of sedation procedure (min), median (range) IQR	11 (4–33) 9–14	10 (5–36) 8–13	0.35 (−1.76 to 2.51)
% patients reporting pain during procedure (95% CI)	2.1 (−2.2 to 6.4)	6.0 (2.7 to 21.3)	−3.8 (−11.9 to 0.4)
% patients reporting recall of the procedure (95% CI)	12.8 (2.9 to 22.7)	12.0 (2.7 to 27.3)	0.8 (−12.7 to 14.2)
% patients reporting satisfaction with the procedure	100	100	
Recovery agitation	17 (36.2)	4 (8.0)	28.2 (12.4 to 43.9)
Time to return to baseline mental status, median (range) IQR	14 (2–47) 10–29	5 (0–32) 4–12	9.38 (5.28 to 13.48)

$ETCO_2$ = end-tidal carbon dioxide; IQR = interquartile range; OAAS = modified observer's assessment of alertness score; sBP = systolic blood pressure.

of clinical interventions associated with respiratory depression between the two groups. Previous studies of ketamine have used different methods of measurement of respiratory depression, making direct comparison difficult. Capnography has been used as a measure of ventilation in several studies of ketamine sedation in children.[24,27,28] In the study by Kim et al.[27] there were no changes in $ETCO_2$ detected after ketamine administration. In the study by Yldzdas et al.[28] comparing propofol and ketamine, a difference was found in the $ETCO_2$ values after ketamine administration, and the rate of patients with a value of >50 mm Hg was 25% lower for ketamine than for patients who received propofol. In light of the results of these small preliminary studies, we assumed we would be able to detect a large difference in the rates of subclinical respiratory depression between ketamine and propofol (the study was designed assuming a 25% decrease from previously reported rates for propofol) and that the most important clinical question we could answer with our study was whether the decreased rate of respiratory depression could justify the rate of recovery agitation, especially when considering which agents to use in patients at risk of complications from respiratory depression. We were surprised to find ketamine had a rate of subclinical respiratory depression higher than that for propofol.

In a previous study of ketamine in adults, Chudnofsky et al.[16] found a rate of respiratory compromise of 6%. This measurement was obtained largely through the judgment of a respiratory therapist monitoring the patient. While this measurement is clearly a valid measure of respiratory compromise, it is unlikely to be sensitive to small changes and is subject to the judgment of various individuals, making it difficult to compare to our study. We measured every clinical intervention that could be associated with respiratory depression, which is much different from measuring patients felt to have compromise, many of whom likely did not have any respiratory compromise after some intervention prevented it. We cannot make comparisons between the respiratory depression associated with ketamine in our study and that seen with previous studies of the use of ketamine in adults.

Table 4
Clinical Signs of Respiratory Depression

	Ketamine (n = 47)	Propofol (n = 50)	Comparison p value	% Difference (95% CI)
Increased supplemental oxygen, n (%)	17 (36.2)	18 (36.0)	0.99	0.2 (−19.4 to 19.7)
Airway adjunct used, n (%)	5 (10.9)	9 (18.0)	0.32	−7.1 (−21.5 to 7.3)
Airway repositioning, n (%)	9 (19.1)	9 (19.0)	0.88	1.1 (−14.7 to 17.0)
Stimulation to induce breathing, n (%)	6 (12.8)	13 (26.0)	0.10	−13.2 (−299.2 to 2.7)

There are, however, multiple studies using these same respiratory depression criteria for propofol, and it is by these that we may compare our work to previous studies. The rate of clinical interventions and subclinical respiratory depression found for propofol in this study is similar to those of previous works using these measurement criteria for propofol.[6,7,19,22,29] We can therefore use this study to put IV ketamine in a similar context to what is known about propofol for procedural sedation in the ED and use this work to perform future evaluations of the use of ketamine.

Clinical interventions related to respiratory depression were not different between the two groups. The relative importance of one clinical intervention over another is not known, nor is the relation of such events to adverse events. These events can only be used to quantify the need for intervention during sedation. Our study is too small to detect true respiratory complications of sedation, but the clinical interventions we observed are likely to be good indications of the potential for respiratory compromise using these drugs. These results suggest that the use of ketamine in place of propofol sedation does not reduce the incidence of respiratory depression or the occurrence of clinical interventions related to respiratory depression.

The depth of sedation by OAAS scale and the rate of success between the two agents appear to be similar. Ketamine, however, showed a longer time to regain baseline mental status after the procedure had been completed. There was no difference in reported recall between the two groups. There was, however, a slightly higher rate of reported pain in the propofol group than in the ketamine group. This may indicate a trend of increased pain among patients who receive propofol that this study was too small to detect. Given that ketamine is known to have analgesic and amnestic properties, and propofol is only known to have amnestic effects, this seems possible. In light of the fact that ketamine is known to have analgesic effects and propofol is not, it appears that patients in the propofol group may have experienced more pain despite not having recall of the pain. In the absence of recall of the procedure, it must be assumed that the reported pain occurred after the period of amnesia induced by the medications. Propofol has been shown to induce 15 minutes of amnesia at these doses.[11] It is likely that the analgesic effects of ketamine persist longer than its amnestic effect, and it is possible that patients in the ketamine group experienced superior analgesia in the time period immediately after the offset of amnesia. This would indicate, as is generally assumed, that patients receiving propofol experienced pain that they did not later recall.

The negative effects of pain are well known and have principally been defined in studies of surgical procedures. The procedures in this study were shorter and less extensive than the painful surgical procedures typically associated with the surgical stress response and postprocedure hyperalgesia,[9] and it is difficult to determine the clinical importance of this possibility. The NMDA receptor is thought to play a central role in central sensitization and post-procedure hyperalgesia after acute pain.[30] As an NMDA receptor antagonist, ketamine is an agent that seems likely to prevent central sensitization after a painful procedure; however, the amount and duration of pain that induces such negative responses and the amount of ketamine needed to prevent these responses is not known, and this benefit remains theoretical.

The rate of recovery agitation was higher among patients who received ketamine than those who received propofol. Only four of the patients who had recovery agitation required treatment for the condition, and these events did not constitute serious adverse events; however, they may have had a role in the increased recovery time of the ketamine group. The median recovery time of subjects who experienced recovery agitation was 20 minutes (range = 2–45 minutes), compared to 8 minutes (range = 1–47 minutes) in those who did not demonstrate recovery agitation. The increased time to the return of baseline mental status does not represent an adverse event; however, an increased need for monitoring after the procedure is not of any benefit to the patient and potentially makes ketamine less useful for ED procedural sedation than propofol.

The lowest blood pressure recorded was higher in the ketamine group than in the propofol group, suggesting that ketamine has less of a negative effect on blood pressure. While we did not detect a difference in the change in blood pressure from baseline between the groups, it may be that further study of ketamine in patients at risk for hypotension (e.g., ASA Physical Status score 3 and 4 patients) would find this effect to be more pronounced and clinically relevant.

LIMITATIONS

There are two principal limitations to our trial. The first is that we did not blind patients, physicians, or data collectors to the agents used. All of the physicians who enrolled patients in this study are familiar with both propofol and ketamine and likely had preconceived

notions about the two agents. The intention of the study was to compare the use of these agents as part of two clinical sedation protocols, rather than the nature of the agents, which are both well defined. Because the success and safety of procedural sedation is operator dependent, we felt that knowledge of the agents is an important clinical factor in decisions about clinical interventions and sedative dosing, and including their effect in our measurements more accurately represents the procedures being studied. Supplemental oxygen was given more frequently in the propofol group than in the ketamine group, likely due to this bias. Our measures of respiratory depression, however, rely principally on changes in $ETCO_2$. Furthermore, supplemental oxygen has not been shown to change the occurrence of respiratory depression,[31] and we do not feel that this bias justified using a less clinically relevant model of a blinded drug.

It is important to note, however, that significantly more patients in the propofol group received supplemental oxygen than in the ketamine group (86% vs. 53%). The rate of the oxygen saturation below 92% was similar between the groups (12.7% vs. 14%), and the lowest O_2 saturation was also noted with propofol (45% vs. 67%). It is possible that, had the use of supplemental oxygen been the same in the two groups, patients in the ketamine group may have exhibited improved oxygenation over patients in the propofol group. Standardization of the use of supplemental oxygen in future studies will likely result in a more accurate comparison of the oxygenation between the sedative agents.

Capnography is robust to differences in the use of supplemental oxygen,[25,31] however, and demonstrates ventilator patterns, making it useful for the monitoring of ventilation during procedural sedation. Declining ventilatory efficiency likely detects increasing airway depression that eventually may lead to aspiration if the patient were to vomit, an adverse event that clearly would lead to poor outcomes in procedural sedation. Hypoxia, however, is a well-recognized adverse event during procedural sedation and an important comparison between groups, despite the fact that it is difficult to link isolated hypoxia to poor outcomes after sedation procedures. While the clinical importance of transient hypoxia during sedation is not known, it can be reasonably assumed that it is not in the patient's best interest and should be avoided.

The second principal limitation is in the outcome measures. In the relative absence of significant adverse outcomes in procedural sedation studies of this size, it is unclear what the optimal measures of respiratory depression and safety are. A wide range of outcome measures have been suggested for sedation research, and all have significant limitations. In the case of subclinical respiratory depression, our criteria have been used in several studies from our institution, and we chose to measure them in this study to maintain internal validity among our studies. We added the use of clinical interventions related to respiratory depression to better capture clinical interventions rather than changes in monitor parameters. While these events may have more clinical validity than the measures of subclinical respiratory depression, they remain at the discretion of the treating physician and as such are subject to the variations in clinical practice among physicians in the study. The decision to intervene during sedation is not necessarily related to the occurrence of an adverse event or the actual need for such an intervention, but to the perception of such need by the treating emergency physician. This is clearly an important factor, but due to its subjective nature, we feel that such events are better described in the context of associated changes in capnographic and pulse oximetry data.

CONCLUSIONS

Our study suggests that using either ketamine or propofol is a safe and effective approach to procedural sedation in the ED. The use of ketamine in place of propofol for procedural sedation resulted in a higher rate of subclinical respiratory depression and a longer time to return of baseline mental status after the procedure and did not result in a difference in recall of the procedure. There was an increased report of pain from the procedure among patients in the propofol group, but our study was too small and the rate too infrequent to allow us to draw conclusions from this. Recovery agitation was seen more frequently in patients receiving ketamine than in those receiving propofol. The use of ketamine for procedural sedation in adults may not be as beneficial as propofol.

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