

Ketamine in Adult Emergency Medicine: Controversies and Recent Advances

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A number of painful and unpleasant procedures are performed in the emergency department (ED) that require sedation and analgesia. Some include direct current cardioversion, closed reduction of orthopedic injuries, and abscess incision and drainage.¹⁻³ In addition, patients requiring endotracheal intubation often undergo this procedure using a rapid sequence intubation (RSI) technique, which is a process involving the administration of a sedative induction agent and a paralytic agent.⁴ It is inhumane to perform these procedures without optimal pharmacotherapy interventions to minimize pain and anxiety. Furthermore, without pharmacotherapy interventions, optimal conditions in which to perform these procedures will not be achieved, which is difficult for both the patient and the health care provider. The ideal agent for both procedural sedation and analgesia (PSA) and RSI should have a rapid onset of action, as well as a sufficient duration of action. It should also allow for rapid recovery with minimal adverse effects. Unfortunately, the ideal pharmacotherapeutic agent has not been found; however, a number of medications provide some of these properties. Traditionally, midazolam,

OBJECTIVE: To review the evidence for the use of ketamine in adult emergency medicine for procedural sedation and analgesia (PSA) and rapid sequence intubation (RSI), as well as to focus on the issues of recovery agitation, combination with propofol for PSA, and the use of ketamine as an induction agent in patients with acute head injury in need of definitive airway management.

DATA SOURCES: PubMed (1949-July 2011), EMBASE (1980-July 2011), Google Scholar (to July 2011), *International Pharmaceutical Abstracts* (1964-July 2011), and Cochrane databases were searched independently. A manual search of references was also performed.

STUDY SELECTION: English-language, full reports of experimental and observational studies evaluating ketamine in adults undergoing PSA and RSI in the emergency department (ED) were included if they reported efficacy or safety outcomes.

DATA EXTRACTION: Two reviewers independently assessed each article for inclusion, data extraction, and study limitations.

DATA SYNTHESIS: Six studies that used ketamine for PSA were included. The majority reported adequate sedation with high patient satisfaction and lack of pain and procedural recall. There is no evidence to support the superiority of a combination of ketamine and propofol compared to propofol alone for PSA in adults. Recovery agitation is common but can be minimized with premedication with midazolam (number needed to treat 6). Two studies were identified that evaluated the role of ketamine for induction during RSI in the ED. Although ketamine is not a first-line agent for RSI, it is an alternative and may be used as an induction agent in patients requiring endotracheal intubation.

CONCLUSIONS: Ketamine is an effective agent in adults undergoing PSA and RSI in the ED. The best available evidence provides sufficient confidence to consider use of this agent in the ED.

KEY WORDS: emergency medicine, intubation, ketamine, procedural sedation and analgesia.

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propofol, or etomidate has been used as the primary agent to facilitate PSA and RSI in the ED.¹⁻⁴

In the practice of emergency medicine, ketamine possesses several alluring pharmacologic characteristics for use during PSA and as an induction agent in RSI.^{5,6} Ketamine is categorized as a dissociative agent, since it causes a functional and electrophysiologic dissociation in the brain. This dissociation creates a trancelike cataleptic state, resulting in profound analgesia and amnesia, with retention of protective airway reflexes, spontaneous respirations, and cardiopulmonary stability.^{5,7,8}

Pharmacologically, ketamine exerts its dissociative effects in the thalamocortical and limbic central nervous system (CNS) by noncompetitively inhibiting glutamate at the *N*-methyl-D-aspartate (NMDA) receptors.⁵ This action predicates its success as a sedative drug; however, its ability to cause confusion between real and imaginary stimuli contributes to the adverse recovery reactions (eg, dreaming, nightmares, hallucinations).^{9,10} Ketamine is also known to stimulate CNS outflow and decrease catecholamine reuptake thought to be responsible for increases in cerebral blood flow, blood pressure, and heart rate, as well as bronchodilation.⁵ Ketamine is highly lipophilic and therefore efficiently crosses the blood-brain barrier.⁵ When given intravenously, the dissociative dose of 1-2 mg/kg has an onset of action of approximately 30 seconds, with an elimination half-life of 2-4 hours.¹¹ The parent compound is metabolized in the liver to an inactive metabolite, norketamine.^{5,11}

Although ketamine has been available for anesthetic purposes since the 1960s, there has been a lack of published literature evaluating its use in the adult ED setting. The majority of research had been performed in the pediatric population.^{5,6,12} Over the past decade, there has been more evidence of both the effectiveness and safety of its clinical use in adults, which has resulted in increased use in the adult ED setting.^{7,10,13} Despite the mounting evidence for its use, some reports suggest that ketamine is used less than 5% of the time for adult PSA in the ED in both academic and community institutions in Canada.^{14,15} Ketamine is not routinely used as an induction agent to facilitate RSI. However, it is often considered in patients being intubated for status asthmaticus and those with hemodynamic instability.^{4,16} This may not be a reflection of a negative or ill-informed impression of ketamine but of more attractive induction agents such as etomidate or propofol that are considered first-line for this indication.

A number of issues have emerged with ketamine use in the ED. Approaches to minimizing recovery agitation, which may occur in up to 30% of patients, remain an area of debate.¹⁰ The use of ketamine in combination with propofol for PSA has received recent attention. The theoretical benefit of administering 2 agents at lower doses to achieve desired clinical endpoints while avoiding unwanted adverse events has yet to be definitively supported.¹⁷ Much debate remains over the use of ketamine as an induc-

tion agent in RSI for patients with acute head injury. The uncertainty in this clinical context results from a lack of research specific to acute head injury in the ED; therefore, conclusions and recommendations have been extrapolated and expostulated from a variety of literature sources.^{18,19} Many of the properties of ketamine, including free radical scavenging, maintenance of hemodynamics (with preservation of cerebral perfusion pressure), and its NMDA blocking properties, make it an attractive, yet unproven, induction agent in airway management following acute head injury.

The purpose of this article is to review the evidence for the use of ketamine in emergency medicine in the context of PSA and RSI in the adult patient population. The review focuses particular attention on the issue of recovery agitation, combination with propofol for PSA, and use of ketamine as an induction agent in patients with acute head injury in need of definitive airway management.

Data Sources

PubMed (1949-July 2011), EMBASE (1980-July 2011), Google Scholar (to July 2011), *International Pharmaceutical Abstracts* (1964-July 2011), and Cochrane databases were searched. Separate searches were conducted using combinations of the terms ketamine, procedural, sedation, intubation, and head injury. The search was restricted to studies on adults in full-text, English-language publications. A manual search of references was also performed. Experimental and observational studies of adults undergoing PSA or RSI in the ED were also included if they reported efficacy or safety outcomes.

Procedural Sedation and Analgesia

Table 1 outlines the details of 6 articles that reviewed the role of ketamine for adult PSA in the ED.^{6,12,20-23} Chudnofsky et al. reported a prospective case series in 77 patients to describe the characteristics of combining intravenous midazolam 0.07 mg/kg followed by intravenous ketamine 2 mg/kg 2 minutes later for PSA in the ED.²⁰ Adequate sedation was achieved with a mean (SD) midazolam dose of 5.6 (1.4) mg and ketamine dose of 159.1 (42) mg. The average (SD) time to achieve alertness sufficient for discharge was 63.4 (23.4) minutes. Five patients experienced mild emergence reactions of less than 30 minutes, causing minimal patient distress, requiring no intervention, and not affecting disposition. Overall, 18 patients (25.7%) could remember having dreams; most (66%) were described as pleasant. Hemodynamically, there was a mean increase in blood pressure and heart rate of 26/19 mm Hg and 21 beats/min, respectively.

Gorchynski et al. conducted a prospective case series in 90 patients undergoing PSA in the ED to evaluate time to sedation and recovery following the use of propofol (42%), ketamine (42%), or midazolam/fentanyl (16%).²¹ The mean

times to sedation, defined as time from first dose to a drowsy, delayed, responsive state reported for propofol, ketamine, and midazolam/fentanyl groups were 4.5, 10.6, and 11.5 minutes, respectively. The mean times to recovery, defined as awake and responsive to stimuli, were 21.6, 55.4, and 59.9 minutes for the 3 groups, respectively. This series did not report safety outcomes.

Newton and Fitton performed a single-center, prospective cohort study in 92 patients receiving intravenous ketamine

0.5-1 mg/kg for PSA in the ED.⁶ Mean increases in systolic blood pressure and heart rate from baseline were found to be 25 mm Hg and 30 beats/min, respectively. Vomiting was reported in 4 patients and hypersalivation and clonic movement in 4 patients. Recovery agitation was experienced by 12 patients (13%).

Vardy et al. reported results of a prospective audit in 210 patients undergoing PSA to assess the efficacy and safety of ketamine compared to propofol and midazolam.²² Medi-

Table 1. Studies Evaluating Ketamine for Procedural Sedation and Analgesia in Adults in the Emergency Department

| Study | Design | Population | Exposure/ Intervention | Outcome |
|---------------------------------|--------------|--|---|--|
| Chudnofsky (2000) ²⁰ | P, O | N = 77 Age 18-68 years (median 28.5) Orthopedic: 26% Abscess I&D: 66% Other: 8% | Midazolam 0.07 mg/kg iv followed 2 minutes later by ketamine 2 mg/kg iv | Mean (SD) dose midazolam 5.6 (1.4) mg ketamine 159 (42) mg Mean (SD) discharge recovery time: 63.4 (23.4) min Mean (SD) BP increased 26/19 (15/12) mm Hg Mean (SD) HR increased 21 (15) beats/min Apnea: 3 (3.9%) Laryngospasm: 1 (1.3%) Recovery agitation (all mild): 5 (6.5%) Dreams: 18 (25.7%) |
| Gorchynski (2006) ²¹ | P, O | N = 90 children and adults | Propofol: 38 (42%) Ketamine: 38 (42%) Midazolam/fentanyl: 14 (16%) Doses not reported | Mean (SD) time to sedation propofol 4.5 (1.2) min ketamine 10.6 (4.8) min midazolam/fentanyl 11.5 (7.9) min Mean (SD) time to recovery propofol 21.6 (5.5) min ketamine 55.4 (9.2) min midazolam/fentanyl 59.9 (39.6) min |
| Newton (2008) ⁶ | P, O | N = 92 Age 16-89 years Orthopedic: 95% Abscess I&D: 3.2% Other: 2.1% | Ketamine 0.5 mg/kg iv, followed by 0.5 mg/kg iv as necessary 5 minutes later | Mean (SD) dose: ketamine 0.7 (0.3) mg/kg Adequate sedation: 91 (98.9%) Procedural success: 100% Recovery agitation: 12 (13.0%); 5 transient, with no intervention; 7 given midazolam |
| Vardy (2008) ²² | P, O (audit) | N = 210 Age 11-103 years (mean 49); ≤16 years: 8 Orthopedic: 94% Abscess I&D: 3% Other: 3% | Ketamine: 85 (40%) Midazolam: 107 (51%) Propofol: 18 (9%) | Median dose (range) ketamine 65 mg (6-180) midazolam 5 mg (2-20) propofol 100 mg (20-200) Median recovery time ketamine 25 min midazolam 30 min propofol 10 min Recovery agitation 17 (8.1%) of total population 16/85 (18.8%) of those taking ketamine |
| Sim (2008) ²³ | P, O | N = 15 Age 19-45 years (mean 29) Abscess I&D: 100% | Midazolam 2-5 mg iv followed 2 minutes later by ketamine 2 mg/kg | Mean dose midazolam 3.2 mg ketamine 2 mg/kg Mean (SD) time to recovery: 187 (138) min Recovery agitation: 1 bad dream with no agitation |
| Miner (2010) ¹² | P, RCT, OL | N = 97 Age 18-85 years Orthopedic: 53% Abscess I&D: 41% Cardioversion: 1% Other: 4% | Ketamine 1 mg/kg iv, then 0.5 mg/kg every 3 minutes as necessary vs Propofol 1 mg/kg iv, then 0.5 mg/kg every 3 minutes as necessary | Median dose (range) ketamine 1.00 mg/kg (0.85-3.00) propofol 1.46 mg/kg (0.65-3.80) Median time to sedation (range) ketamine 11 min (4-33) propofol 10 min (5-36) Subclinical respiratory depression ketamine 63.8% vs propofol 40% (p = 0.02) No difference in clinical interventions Recovery agitation: 17 (36.2%) ketamine: 4 given midazolam 4 (8.0%) propofol |

BP = blood pressure; HR = heart rate; I&D = incision and drainage; O = observational; OL = open-label; P = prospective; RCT = randomized controlled trial.

an times to recovery for ketamine, midazolam, and propofol were 25, 30, and 10 minutes, respectively. Ketamine and propofol were comparable with respect to level of sedation, while midazolam appeared to be inferior to both agents. Adverse events were reported, with an incidence of 14.6% with ketamine, 15.8% with midazolam, and 22.2% with propofol. Midazolam and propofol were responsible for more apnea and hypoxia; ketamine was associated with more hypertonicity, hypertension, and emergence reactions.

Sim and Seet conducted a prospective observational case series of 15 patients requiring abscess incision and drainage.²³ Patients were given intravenous midazolam 2-5 mg, followed by intravenous ketamine 2 mg/kg. The mean (SD) time to recovery was 187 (138) minutes. One of the 15 (6.7%) patients reported experiencing an unpleasant dream with no agitation.

Miner et al. performed the only prospective randomized trial in adults undergoing PSA in the ED.¹² This nonblinded study of 97 patients compared intravenous ketamine 1 mg/kg (titrating doses 0.5 mg/kg every 3 minutes) to intravenous propofol 1 mg/kg (titrating doses 0.5 mg/kg every 3 minutes). Each group was able to receive morphine for analgesia up to 20 minutes before the procedure. The ketamine group was not premedicated with midazolam as part of the regimen. The median ketamine dose was 1 mg/kg, with the majority requiring only the single dose to achieve adequate sedation. The propofol group had a median dose of 1.46 mg/kg. The primary outcome of this study was to assess subclinical respiratory depression, defined as a change in baseline end-tidal carbon dioxide (ETCO₂) higher than 10 mm Hg, oxygen saturation less than 92% at any time during the procedure, or absent ETCO₂ waveform. The primary outcome was observed in 63.8% of the ketamine group and 40.0% of the propofol group (absolute risk reduction [ARR] 23.8%, number needed to treat [NNT] 5; $p = 0.02$). Clinical interventions related to respiratory depression did not differ between groups. Notably, the propofol group required more interventions (propofol 52% vs ketamine 40%, $p = \text{NS}$). Both groups reported satisfaction with the procedure and a similar percentage of recall (~12%), while pain was reported in 2.1% of the ketamine group compared to 6.0% of the propofol arm. There were no serious adverse effects found in the study. Recovery agitation was reported in 36.2% of patients who received ketamine, compared to 8.0% of those who received propofol (absolute risk increase 28.2%, number needed to harm 4).

The majority of published literature evaluating ketamine for adult PSA is derived from observational trials. A common limitation of observational studies is their inability to control and adjust for confounders.^{6,20-23} They also assessed subjective endpoints, each with unique measurement tools

created for the purpose of their own studies. Heterogeneity exists between studies with regard to ketamine dosing and the definition of *adequate sedation*, making it difficult to compare the analysis as a sum effect of ketamine. Chudnofsky et al.²⁰ and Sim and Seet²³ started with a much higher dose of ketamine (2 mg/kg) than is often used in current practice. In addition, this difference was compounded, as they coadministered midazolam with every ketamine dose. Chudnofsky et al.²⁰ dosed midazolam at 0.07 mg/kg, which is higher than is usually used for premedication and may explain the 3 cases of apnea in this study. Gorchynski et al.²¹ failed to report any information on doses or method of administration, precluding conclusions based on their endpoints of time to sedation and recovery.

Although the trial by Miner et al. was randomized, there was a difference between baseline groups.¹² In the propofol group, 86% received supplemental oxygen before the procedure, compared to 53% in the ketamine arm. This has particular confounding potential because the primary outcome included oxygen saturation less than 92% as a measure of subclinical respiratory depression. The authors addressed this issue and stated that it may have played a role in the outcome of poorer oxygenation in the ketamine arm. Secondly, it must be questioned whether the study's primary endpoint of subclinical respiratory depression has any clinical significance, especially in the context of having no significant difference in clinically relevant adverse events and a higher incidence of interventions in the propofol group.

RECOVERY AGITATION

The aforementioned studies describe variable incidence and degree of recovery agitation (Table 1). Furthermore, there were methodologic differences between studies regarding the use of midazolam as a preventative measure. Sener et al. recently reported the only prospective, randomized, double-blind, placebo-controlled trial in 182 patients undergoing PSA in the ED to evaluate the efficacy of coadministration of midazolam and ketamine to prevent recovery agitation.¹⁰ Patients were randomized to either intravenous ketamine 1 mg/kg or intramuscular ketamine 4 mg/kg with or without intravenous midazolam 0.03 mg/kg administered 2 minutes prior to ketamine. The incidence of recovery agitation in patients receiving intravenous ketamine with or without midazolam was 7% and 22%, respectively. The intramuscular ketamine route with or without midazolam resulted in recovery agitation in 9% and 28% of patients, respectively. When the intravenous and intramuscular routes were combined, there was a 17% ARR in recovery agitation when midazolam premedication was given (NNT 6) compared to no midazolam. This is the best available evidence and supports the coadministration of midazolam 0.03 mg/kg to adults receiving ketamine for PSA.

PROPOFOL/KETAMINE COMBINATION

In 2007 Slavik and Zed reviewed the available evidence on the use of the combination of ketamine plus propofol to perform PSA.¹⁷ Eight randomized trials were appraised that met the inclusion criteria of using a propofol/ketamine combination for PSA. None of these studies was performed in the ED. Propofol/ketamine was compared to propofol alone in 7 studies, and 1 study compared propofol/ketamine to propofol/fentanyl. The authors noted that the studies were small, with significant heterogeneity between methodology and doses, and concluded that there is not enough evidence to suggest that the combination of ketamine and propofol is more efficacious than propofol monotherapy. In addition, the combination had not been compared to ketamine monotherapy. There was also no compelling evidence that hemodynamic stability, respirato-

ry depression, or any other adverse events were less common with propofol/ketamine. More postprocedure nausea and vomiting, visual disturbances, and dreams occurred when the combination of propofol/ketamine was used in ratios close to 3.3:1 mg.

Table 2 outlines the studies evaluating propofol/ketamine combinations for PSA in the ED. Willman and Andolfatto conducted a prospective case series and were the first to describe the use of propofol/ketamine in the ED.²⁴ They administered propofol/ketamine in a 1:1 ratio mixed in the same syringe (median dose 0.75 mg/kg); patients could receive opioids prior to the procedure at the discretion of the physician. Of the 114 procedures attempted, 96% required no adjunct medications to complete the procedure. The median recovery time for propofol/ketamine was 15 minutes (range 5-45). Apnea occurred in 3 patients: bag-valve-mask ventilation was required for 1 pa-

Table 2. Studies Evaluating Propofol/ketamine Combination for Procedural Sedation and Analgesia in Adults in the Emergency Department

| Study | Design | Population | Exposure/ Intervention | Outcome |
|---------------------------------|--------|--|--|---|
| Willman (2007) ²⁴ | P, O | N = 114 Age <16 years: 25; ≥16 years: 89 Orthopedic: 69.3% Abscess I&D: 11.4% Cardioversion: 7.9% Other: 11.4% | Ketamine 10 mg/propofol 10 mg mixed in the same syringe Dose titrated to attain deep, dissociative sedation | Median dose (range): propofol/ketamine 0.75 mg/kg (0.2-2.05) Median recovery time (range): 15 min (4-45) Procedure success: 96% Required additional propofol doses: 2.6% Unable to complete procedure: 0.9% Hypoxia: 2.6% (1 requiring bag-valve-mask ventilation) Emergence reaction: 0.9% (treated with midazolam) |
| Andolfatto (2011) ²⁵ | P, O | N = 728 Age 37-70 years (median 53) Orthopedic: 68% Abscess I&D: 13% Cardioversion: 11% Other: 8% | Ketamine 10 mg/propofol 10 mg mixed in the same syringe Dose titrated to attain deep, dissociative sedation | Median dose (range): propofol/ketamine 0.70 mg/kg (0.2-2.7) Median recovery time (range): 14 min (3-50) Procedure success: 98% Required additional propofol doses: 1.2% Unable to complete procedure: 0.1% Airway intervention: 2.9% Transient dysrhythmias: 0.5% Recovery agitation: 3.6% |
| Messenger (2008) ²⁶ | P, RCT | N = 63 Age 14-65 years Orthopedic: 96.9% Abscess I&D: 3.1% | Ketamine 0.3 mg/kg iv vs Fentanyl 1.5 µg/kg iv All received propofol 0.4 mg/kg iv 2 minutes later Additional propofol 0.1 mg/kg boluses until responsive only to deep stimuli | Intersedation adverse events: 46.8% ketamine vs 83.9% fentanyl (ARR 37.1%, NNT 3) |
| Phillips (2010) ²⁷ | P, RCT | N = 28 Adults | Ketamine 0.5-1 mg/kg iv plus propofol 0.75 mg/kg iv vs Propofol 0.5-1 mg/kg iv | Bispectral Index Scale: 77 (8 SD) propofol/ketamine vs 61 (11.4) propofol (p < 0.0004) Total propofol used: propofol/ketamine 93 mg vs propofol 177 mg (p < 0.32) Lowest systolic BP: propofol/ketamine 139 (22) mm Hg vs propofol 118.3 (13.3) mm Hg (p < 0.326) Vivid dreams: 3 propofol/ketamine users Transient disorientation: 1 propofol user |
| David (2011) ²⁸ | P, RCT | N = 193 Age ≤18 years: 98; <18 years: 93 Orthopedic: 88% Abscess I&D: 2.5% Suturing: 7.5% Other: 8% | Ketamine 0.5 mg/kg iv vs placebo All received propofol 1 mg/kg iv Additional propofol 0.5 mg/kg boluses allowed All received fentanyl 0.5 mg/kg or 1 mg/kg 5 minutes preprocedure | Respiratory depression propofol/ketamine: 22% propofol: 28% Total propofol used (range) propofol/ketamine: 100 mg (14-450) propofol: 175 mg (20-730) |

ARR = absolute risk reduction; BP = blood pressure; I&D = incision and drainage; NNT = number needed to treat; O = observational; P = prospective; RCT = randomized controlled trial.

tient, while 2 required repositioning, stimulation, and supplemental oxygen. A fourth patient experienced recovery agitation and required midazolam.

The same authors published a subsequent case series in 728 adults that used the same 1:1 mg propofol/ketamine single-syringe method.²⁵ A median dose of 0.7 mg/kg was required for physician-judged adequate sedation, which was effective in nearly all (98%) patients. The median recovery time was 14 minutes (range 3-50). Airway interventions were required in 21 (2.9%) patients, while 4 patients experienced transient dysrhythmias. Recovery agitation occurred in 26 (3.6%) patients, half of whom required treatment with midazolam. Clinicians reported being very satisfied with the combination intervention, and 97% of patients reported that they would prefer propofol/ketamine for a future PSA.

Messenger et al. performed a prospective, randomized, double-blind trial evaluating the frequency of cardiorespiratory events and interventions when using ketamine versus fentanyl in 63 patients receiving propofol for PSA in the ED.²⁶ The patients were randomized to either intravenous ketamine 0.3 mg/kg or intravenous fentanyl 1.5 µg/kg. After 2 minutes, all patients received intravenous propofol 0.4 mg/kg, after which they were able to receive additional doses of intravenous propofol 0.1 mg/kg every 30 seconds as needed for adequate sedation. A 10-point intersedation rating scale was developed to assess the patient at baseline, during the procedure, and postprocedure. Intersedation adverse events occurred in 83.9% of patients in the fentanyl group compared to 46.8% in the ketamine arm (ARR 37.1%, NNT 3). When analyzed separately, each adverse event was consistently experienced more frequently by the fentanyl group. Subsequent propofol doses were used more often in the ketamine group (mean difference 0.4 mg/kg). Other parameters, including indicators for sedation efficacy, recovery time, patient pain, and recall, did not differ between groups.

Phillips et al. performed a prospective, randomized, controlled trial that compared ketamine plus propofol to propofol alone in 28 patients undergoing PSA in the ED.²⁷ The intravenous ketamine doses were higher in this study, ranging from 0.5 to 1 mg/kg, with propofol 0.75 mg/kg. The comparator intravenous propofol doses ranged from 0.5 to 1.5 mg/kg. The primary outcome was adequacy of sedation measured using the bispectral index scale (BIS), which is not routinely used in clinical practice. The propofol/ketamine group displayed less of a difference in BIS between baseline and goal sedation. Thus, the authors suggested that adequate sedation with propofol/ketamine was achieved without the need for deep sedation compared to propofol alone. Safety outcomes revealed significantly less reduction in blood pressure in the propofol/ketamine group. Neither group experienced respiratory depression or a significant difference in length of sedation.

David and Shipp conducted a randomized, double-blind, placebo-controlled trial to compare the frequency of respiratory depression in 98 adults and 93 children receiving a propofol/ketamine combination versus propofol alone for PSA in the ED.²⁸ All participants received an intravenous dose of fentanyl 0.5-1.0 µg/kg 5 minutes before sedation. Patients were given either ketamine 0.5 mg/kg or placebo over 1 minute, followed by a dose of propofol 1 mg/kg over 2 minutes. Bolus doses of propofol 0.5 mg/kg were given as needed to maintain a Colorado Behavioral Numerical Pain Scale of 0 (restful, no facial expression). The level of sedation achieved was similar in both groups and there was no significant difference between the 2 treatment groups for the primary outcome of respiratory depression. Subjectively, there was a significant difference in the reported overall satisfaction of the quality of the sedation, with 95% of physicians being satisfied with propofol/ketamine compared to 65% satisfied with propofol alone. There were no reported occurrences of emergence reactions or other adverse drug events.

The combination of propofol/ketamine has failed to demonstrate any efficacy or safety advantage compared to propofol alone.¹⁷ The majority of studies evaluating the role of propofol/ketamine for PSA were not performed in the ED. The best available evidence evaluating the use of propofol/ketamine is derived from the trials by Messenger et al.²⁶ and David and Shipp,²⁸ which administered subdissociative doses of ketamine prior to propofol administration. Messenger et al. reported a lower rate of intersedation adverse events in the propofol/ketamine group compared to patients who received propofol/fentanyl; however, they failed to address the value of the propofol/ketamine combination compared to propofol or ketamine monotherapy.²⁶ Recent evidence from Miner et al. suggests that opioids may not be necessary in patients receiving propofol for PSA in the ED.²⁹ In a trial of 145 patients undergoing PSA with propofol, reports of pain and procedural recall did not differ significantly among patients who did or did not receive opioids; 94% of patients in both arms reported satisfaction with the procedure. Significantly more patients in the opioid arm experienced absent ETCO₂ waveform (36.6% vs 18.8%, $p = 0.02$) and required stimulation to induce respiration (28.2% vs 14.9%, $p = 0.05$).²⁹ Thus, the lack of a propofol monotherapy arm in the study by Messenger et al. fails to address the importance of any analgesic in PSA.²⁶

Rapid Sequence Intubation

Table 3 summarizes 2 studies that evaluated the role of ketamine for induction during RSI in the ED. Sivilotti et al. performed a multicenter, observational study to evaluate the efficacy of barbiturates, etomidate, ketamine, benzodiazepines, and opioids used during RSI.¹⁶ Drugs were com-

pared by assessing the outcome of successful intubation on the first attempt. Among the emergency medicine practitioners, etomidate was the most commonly used agent (62%), while ketamine was used less frequently (3.1%). Among the agents evaluated, ketamine was associated with a decreased incidence of successful intubation on the first attempt. Safety outcomes were not reported.

The KETASED study was a prospective, randomized trial comparing ketamine and etomidate in RSI in 655 critically ill patients.³⁰ Adults intubated in the ED were randomized to intravenous ketamine 2 mg/kg or intravenous etomidate 0.3 mg/kg; all patients were given intravenous succinylcholine 1 mg/kg. There was no significant difference between study groups in relation to changes in hemodynamic parameters during intubation. The primary outcome assessed was organ failure measured by the maximum sequential organ failure assessment (SOFA) score during the first 3 days of admission. There was no statistically significant difference between study arms with regard to the primary outcome. There were also no significant differences between groups in overall change in SOFA score from baseline or 28-day mortality. Although not significant, a trend was observed suggesting that the ketamine group required fewer days of mechanical ventilation and had more intensive care unit–free days of hospitalization. There were no serious adverse events recorded for either agent.

HEAD INJURY

A group of small observational trials including surgical or neurologic patients with variable dosing of ketamine for RSI were performed in the 1970s and found increases in intracranial pressure (ICP). This result may have been confounded by the fact that many of these patients had cerebrospinal fluid outflow obstruction.¹⁹ The findings have resulted in caution surrounding the use of ketamine in patients with acute head injury.

Filanovsky et al. compared 5 small trials (20–35 patients each) that evaluated ketamine use for indications other than

RSI.¹⁹ These trials were heterogeneous in terms of methodology, types of patients, medications, and doses used. Mayberg et al. saw a statistically significant decrease in ICP after the administration of a 1-mg/kg bolus dose of ketamine in 20 neurosurgical patients.³¹ In patients with moderate-to-severe head injury, Kolenda et al. reported statistically significant but clinically insignificantly higher ICP values (~2 mm Hg) in patients receiving ketamine plus midazolam compared to fentanyl plus midazolam.³² Three subsequent randomized trials found no statistically significant difference in ICP with ketamine compared to non-ketamine regimens.^{33–35} Limitations of the studies on ketamine use in patients with head injury are that they did not take place in the ED setting. Despite the theoretical concerns with ketamine use for induction of RSI in patients with acute head injury, there are no data to suggest it should be contraindicated in patients requiring airway assistance.

Discussion

The best available evidence provides sufficient confidence to generate a definitive approach to the use of ketamine in the ED. Studies evaluating the efficacy and safety of ketamine in adults undergoing PSA in the ED have demonstrated that ketamine provides adequate sedation with a high degree of patient satisfaction and lack of pain and procedural recall. The growing popularity of ketamine in the ED, as well as its unique characteristics, has prompted a drug-specific clinical practice guideline (CPG) for this setting.³⁶ Recommendations from this CPG are consistent with our findings but also cover areas outside the scope of this review, specifically ketamine use in the pediatric patient.

Longer recovery times are observed with ketamine compared to propofol, with most studies reporting mean recovery time of approximately 60 minutes. Patients administered ketamine appear to take longer to regain alertness than with propofol, suggesting a potential advantage of ketamine for longer procedures such as abscess incision and drainage or complicated wound closure. Although various

Table 3. Studies Evaluating Ketamine for Rapid Sequence Intubation in Adults in the Emergency Department

| Study | Design | Population | Exposure/ Intervention | Outcome |
|--------------------------------|----------------|-----------------------------------|---|--|
| Sivilotti (2003) ¹⁶ | P, O | N = 1321 Age ≤12 years: 112 | Sedatives barbiturates: 181 (7.6%) etomidate: 1468 (62%) ketamine: 73 (3.1%) benzodiazepines: 421 (18%) opioids: 45 (1.9%) none: 192 (8.1%) | Successful first ETI barbiturates: OR 2.58 (95% CI 1.48 to 4.50) etomidate: OR 0.88 (95% CI 0.70 to 1.10) ketamine: OR 0.62 (95% CI 0.36 to 1.06) benzodiazepines: OR 0.88 (95% CI 0.67 to 1.16) opioids: OR 2.13 (95% CI 0.76 to 1.60) |
| Jabre (2009) ³⁰ | P, RCT, SB, MC | N = 655 Age ≥18 years | Ketamine 2 mg/kg iv bolus vs etomidate 0.3 mg/kg iv bolus | Intubation conditions did not differ Mean (SD) SOFA _{max} score difference: 0.7% (0.0–1.4) (p = 0.056) 28-day mortality difference: 4% (95% CI –4 to –12) (p = 0.36) |

ETI = endotracheal intubation; MC = multicenter; O = observational; OL = open label; P = prospective; RCT = randomized controlled trial; SB = single-blind; SOFA_{max} = maximum sequential organ failure assessment score.

intravenous dosing approaches have been studied, with doses as high as a bolus of 2 mg/kg, most patients do not require this dose. A smaller intravenous starting dose of 0.5-1 mg/kg is recommended, followed by 0.5 mg/kg as necessary to maintain adequate sedation. In addition, although not specifically studied, ketamine does have advantages in the substance abuse population needing ED procedures, particularly intravenous drug users who are typically tolerant to opioids, benzodiazepines, and propofol.³⁷

Unlike other sedative agents, ketamine has been reported to cause hypertension and tachycardia as a result of stimulation of CNS sympathetic outflow.^{5,11,38} Transient increases in blood pressure and heart rate are consistently reported; however, this effect does not appear to be clinically significant.^{12,20,26} Recovery agitation occurs with ketamine administration, most likely caused by its unique dissociative pharmacologic mechanism. Published data have described a range of incidence from none to 36%.^{6,12,13,20,24,25} Premedication with intravenous midazolam 0.03 mg/kg 2 minutes before administering ketamine is effective in minimizing recovery agitation (NNT 6) and does not appear to result in any increase in respiratory or cardiovascular effect or impair recovery time.¹⁰

The role of propofol/ketamine for PSA remains unclear, despite its clinical popularity. There is no evidence that this combination provides improved outcomes or safety profile compared to either agent alone.

Ketamine used as an induction agent in RSI in emergency medicine has a paucity of supporting literature. Sivilotti et al. reported the reduced odds of achieving a successful first-attempt intubation when using ketamine compared to other agents.¹⁶ When ketamine was directly compared to etomidate for RSI in the critically ill, no significant difference was reported in long-term outcomes of these patients, including mortality.³⁰ Ketamine has not yet achieved status as a first-line agent in emergency medicine RSI, and to date, there has been no evidence to suggest that this should be the case. Further head-to-head trials are required to establish its role.

Ketamine safety for induction of RSI in patients with acute head injury has been debated but poorly studied. Purported contraindication for use in this patient population is derived from trials in which ketamine was not being used for induction in RSI. The recent review of literature by Filanovsky et al. showed no statistically significant difference in ICP with ketamine.¹⁹ In view of the current focus on cerebral perfusion pressure rather than ICP in patients with acute head injury, and the known association between hypotension and poor outcome in this population, the lower incidence of hypotension as a result of ketamine use theoretically makes it an ideal agent in patients who are normotensive or hypotensive and have head injuries or in multitrauma patients with head injuries. The updated 2011 CPG has removed head trauma as a relative contraindication to ketamine because of a lack of evidence to suggest safety concerns.³⁶

This review of the literature of ketamine in emergency medicine highlights a safe and effective drug that may be underutilized in the ED setting, particularly for patients undergoing PSA. It may be an ideal choice as a first-line therapy for longer procedures or for patients with active substance abuse. Although the longer recovery time has been viewed as a negative characteristic, there is no evidence to suggest that this makes a difference in disposition time compared to other agents. Patients with active substance abuse display tolerance to agents such as benzodiazepines and propofol. Although not formally studied, ketamine is an attractive agent in this patient population.

Summary

Ketamine is an effective agent in adults undergoing PSA in the ED setting. Although it appears to be as effective and safe as propofol, it may be a more useful agent for longer procedures or for patients with known substance abuse. The primary safety concern is recovery agitation; however, pretreatment with midazolam reduces the risk of this adverse event. There is no high-level evidence to support the use of propofol/ketamine combinations at this time for PSA. Although ketamine has not been studied extensively as an induction agent in RSI, it possesses excellent pharmacologic properties for use in this clinical scenario and the literature demonstrates no increased harm to the patient when used as an RSI induction agent. There appears to be no significant increase in ICP after the administration of ketamine and thus, given its other properties, we believe it can be used in patients with acute head injury undergoing RSI for tracheal intubation. There is a dearth of high-level evidence regarding ketamine in combination with propofol for PSA and RSI. Ketamine has achieved credibility as an effective and safe agent in the adult ED setting.

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Ketamina en la Emergencia Médica de Adultos: Controversias y Adelantos Recientes

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EXTRACTO

OBJETIVO: El propósito de este reporte es repasar la evidencia que apoya el uso de ketamina como medicamento de emergencia en adultos para la sedación y analgesia procesal (SAP) e intubación de secuencia rápida (ISR). Este reporte también se centrará en cuestiones de agitación de recuperación, combinación con propofol para la SAP y el uso de ketamina como agente inductor en pacientes con lesión cerebral aguda en necesidad de manejo ventilatorio definitivo.

FUENTES DE INFORMACIÓN: Se realizó búsquedas independientes de los bancos de datos de PubMed (1949-julio del 2011), EMBASE (1980-julio del 2011), Google Scholar (hasta julio del 2011), *Abstractos Farmacéuticos Internacionales* (1964-julio del 2011), y Cochrane. Se realizó también una búsqueda manual de las referencias encontradas.

SELECCIÓN DE ESTUDIOS: Se incluyeron publicaciones de eficacia o seguridad en idioma inglés si éstos contenían estudios experimentales y de observación completos que evaluaron el uso de ketamina en pacientes adultos sometidos a SAP e ISR en el departamento de emergencia (DE).

EXTRACCIÓN DE DATOS: Dos revisores evaluaron, de forma independiente, cada publicación para inclusión, extracción de datos e identificación de las limitaciones de los estudios.

SÍNTESIS DE DATOS: Se incluyeron 6 estudios que usaron ketamina para la SAP. La mayoría reportaron sedación adecuada con alta satisfacción del paciente y ausencia de recordación de dolor y procedimiento. Los resultados demuestran que no hay evidencia que apoye que el uso de la combinación de ketamina/propofol sea superior al propofol solo para la SAP en adultos. La agitación de recuperación es común pero puede ser minimizado con el uso de midazolam como pre-medicación (NNT 6; número de pacientes que es necesario tratar). Se identificaron dos publicaciones que evaluaron el rol de ketamina para inducción durante la ISR en el DE. Aunque la ketamina no es un agente de primera línea para la ISR, ésta puede ser una alternativa y puede ser utilizado como agente de inducción en pacientes que requieren intubación endotraqueal.

CONCLUSIONES: La ketamina es un agente eficaz en pacientes adultos sometidos a la SAP e ISR en el DE. La mejor evidencia disponible proporciona suficiente confianza para considerar el uso de este agente en el DE.

Traducido por Carlos C da Camara

Le Recours à la Kétamine en Médecine d'Urgence: Controverses et Avancées Récentes

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RÉSUMÉ

OBJECTIF: Revoir les données probantes sur l'utilisation de la kétamine lors d'une intubation séquentielle rapide ou lors de procédures où une sédation, une amnésie et/ou une analgésie est désirée chez un patient adulte reçu au département d'urgence. Mettre l'emphase sur différents enjeux spécifiques dont notamment les réactions d'agitation au réveil, la combinaison de la kétamine au propofol et l'utilisation de la kétamine comme agent d'induction chez les patients ayant un traumatisme crânien aigu et qui sont en attente d'une gestion définitive des voies aériennes.

SOURCES D'INFORMATION: Une recherche documentaire a été effectuée dans les banques de données PubMed (1949-juillet 2011), EMBASE (1980-juillet 2011), Google Scholar (jusqu'en juillet 2011), *International Pharmaceutique Résumé* (1964-juillet 2011), et Cochrane. Une recherche manuelle de références a aussi été effectuée.

SÉLECTION DE L'INFORMATION: Toutes les études expérimentales et observationnelles publiées en langue anglaise ayant évalué l'efficacité et/ou l'innocuité de la kétamine chez les patients adultes nécessitant une analgésie et/ou une sédation lors de procédures au département d'urgence ont été revues par 2 évaluateurs indépendants.

RÉSUMÉ: La majorité des 6 études évaluées rapporte que la kétamine procure une sédation adéquate ainsi qu'une amnésie appropriée face à la douleur et à la procédure effectuée tout en étant associé à un taux élevé de satisfaction des patients traités. Il n'existe aucune donnée probante documentant une efficacité supérieure d'une combinaison kétamine-propofol par rapport à une monothérapie de propofol. Les réactions d'agitation au réveil sont fréquentes suivant l'administration de la kétamine et peuvent être minimisées avec une prémédication de midazolam (NNT 6). Certaines données ont évalué le rôle de la kétamine lors d'une intubation séquentielle rapide. Bien que la kétamine ne soit pas un agent de première intention dans un tel contexte, elle peut s'avérer une option alternative lorsqu'un agent d'induction est requis chez les patients nécessitant une intubation endotrachéale.

CONCLUSIONS: Il existe plusieurs données probantes documentant l'efficacité de la kétamine pour induire une sédation, une amnésie et/ou une analgésie chez un patient adulte dans un contexte de médecine d'urgence.

Traduit par Sylvie Robert