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Clinical Review

KETAMINE FOR RAPID SEDATION OF AGITATED PATIENTS IN THE PREHOSPITAL AND EMERGENCY DEPARTMENT SETTINGS: A SYSTEMATIC REVIEW AND PROPORTIONAL META-ANALYSIS

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□ **Abstract—Background: Rapid tranquilization of agitated patients can prevent injuries and expedite care. Whereas antipsychotics and benzodiazepines are commonly used for this purpose, ketamine has been suggested as an alternative. Objective: The aim of this systematic review is to determine the safety and effectiveness of ketamine to sedate prehospital and emergency department (ED) patients with undifferentiated agitation. Methods: Studies and case series of patients receiving ketamine for agitation were included. Studies were excluded if ketamine was used for analgesia, procedural sedation, asthma, or induction. Information sources included traditional and gray literature. Results: The initial search yielded 1176 results from 14 databases. After review of titles and abstracts, 32 studies were reviewed and 18 were included in the analysis, representing 650 patient encounters. The mean dose of ketamine was 315 mg (SD 52) given intramuscularly, with adequate sedation achieved in 7.2 min (SD 6.2, range 2–500). Intubation occurred in 30.5% of patients (95% confidence interval [CI] 27.0–34.1%). In the majority of those patients, ketamine was administered by paramedics during ground transport and the patient was intubated on ED arrival. When ketamine was administered in the ED, the intubation rate was 1.8% (95% CI 0.0–4.4%); in air medical transport, the rate was 4.9% (95% CI 0.0–10.3%). Other reported side effects included: vomiting, 5.2% (2.3–8.1%); hypertension, 12.1% (5.7–18.6%); emergence reactions, 3.5% (1.4–5.6%); transient hypoxia, 1.8% (0.1–3.6%) and laryngospasm, 1.3% (0.3–2.3%). Conclusions: Ketamine provides rapid sedation for undifferentiated agitated patients and is associated with higher intubation rates when used by ground Emergency Medical Services paramedics, compared with ED or air medical transport patients. Other side effects are common but usually self-limiting.** © **2018 Elsevier Inc. All rights reserved.**

□ **Keywords—ketamine; excited delirium syndrome (ExDS); acute behavioral disturbance (ABD); agitated; emergency department; laryngospasm; sedation; intubation**

INTRODUCTION

Acutely agitated patients commonly present to the emergency department (ED) or arrive by ambulance; causes are varying combinations of alcohol, drugs, medical problems, and psychiatric exacerbations (1,2). Rapid stabilization is frequently necessary to reduce the risk of injury for staff, bystanders, and the patients themselves (3,4).

The ideal sedative for an agitated patient would have several key properties. It would be easily administered without intravenous access; it would have a very quick onset of action and moderate duration of effect; it would have no hemodynamic effects and would not affect respiratory reflexes; a reversal agent would be available; and it would have a wide therapeutic window so that precise dose calculation is not required in an emergency.

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Traditional agents such as benzodiazepines and antipsychotics have several drawbacks. Benzodiazepines potentiate the risk of respiratory failure when combined with alcohol or other central nervous system depressants that the patient may have consumed (5). In one study, prehospital midazolam administered for agitation was associated with an intubation rate of 37% (6). Butyrophenones, especially haloperidol, are associated with prolongation of the QTc interval (7–9). In one study, when parenteral haloperidol was given to agitated patients, it significantly prolonged the QTc 8 h after administration (8). Prolonged QTc has been associated with torsades de pointes and sudden cardiac death, although the degree of association is unclear. In two separate studies, haloperidol was associated with a 4% intubation rate (10,11).

Traditional antipsychotics and benzodiazepines have onsets of action in 15–30 min (12). Patients with excited delirium syndrome (ExDS, an extreme form of acute behavioral disturbance [ABD]) are prone to develop significant acidosis and are at risk for cardiac dysrhythmias and death (13–16). Because this acidosis may develop over the course of a few minutes, the traditional medications may not act quickly enough to have a useful effect (17). Ketamine, a drug familiar to many emergency physicians, may provide a better alternative.

Ketamine's physiologic function is achieved through binding a number of receptors, chiefly the *N*-methyl-D-aspartate receptor, but also various opioid receptors and interfering with nitric oxide synthesis (18). It can be administered orally, intravenously, intramuscularly, intranasally, or intraosseously. It readily crosses the blood–brain barrier and has a typical onset of action of < 5 min and a duration of 30 min (19).

Ketamine has been used for many indications in the ED, including procedural sedation, pain control, local anesthesia, rapid sequence intubation, and as a bronchodilator for treatment of asthma (20). It has even been used in the psychiatric ED to treat depression (21). In dissociative doses, ketamine causes rapid onset of sedation while preserving airway reflexes, and has been suggested as a primary or secondary agent for the control of agitated patients in the ED. Ketamine causes few hemodynamic changes, even in agitated patients (22). Notable side effects include hypersalivation, laryngospasm, emergence agitation, and respiratory depression. Some studies have shown worsening of both positive and negative symptoms in schizophrenic patients who are administered i.v. ketamine, however, these symptoms largely resolve within 2 h, consistent with metabolism and elimination of ketamine (23). One small study (n = 9) reported occasional increases in hallucinations in schizophrenic patients taking haloperidol up to 8–24 h after administration of ketamine (24).

There have been many individual studies on using ketamine for sedation of agitated patients in the ED and prehospital setting attesting to its safety and efficacy. In 2017, the American College of Emergency Physicians issued a clinical policy endorsing the use of ketamine, stating "the skill set of emergency physicians […] make it a reasonable choice when immediate control of an acutely agitated patient is required for patient and/or staff safety." However, the policy did go on to state that there is only "limited literature for guidance" (25).

Though hundreds of articles exist on the use of ketamine in the ED regarding its effectiveness and side-effect profile for pain and procedural sedation, the medical literature is still relatively sparse regarding the use of ketamine for ABD in the ED (26). For example, data on intubation are conflicting; ketamine has been associated with both an increase and a decrease in intubation of patients with ABD (10,27). As such, the purpose of this study is to answer this question: In patients with [undifferentiated agitation] who are given [ketamine], what are the common [adverse effects, such as intubation] compared with [natural history of patients who don't get ketamine]?

Of course, this particular question has been asked and answered by many individual studies, but none (to our knowledge) have been able to compare data from different settings. A more nuanced question is: Among [agitated patients] who [receive ketamine], which ones are more likely to [be intubated]?

MATERIALS AND METHODS

The Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines were followed in the reporting of this systematic review (28,29). We searched 14 databases representing traditional literature as well as gray literature for relevant information sources (see Table 1).

Gray literature includes reports, conference proceedings, doctoral theses/dissertations, newsletters, technical notes, working papers, white papers, patents, and other literature of sufficient quality to be curated by libraries but not controlled by commercial publishers (i.e., where publishing is not the primary activity of the producing body) (30).

Search criteria were defined by first author (SLM) and were expanded and modified by medical librarians (PR and JK). The list of titles and abstracts were reviewed by SLM for appropriateness. Those deemed appropriate were selected by SLM for review. All databases were searched from the earliest possible date of inclusion until May 2018. We used the free-text terms in all databases and in combination with subject headings when thesauri were a component of a database. We imposed no language restrictions. We included papers that contained original research or described case series of patients that received ketamine for treatment of undifferentiated agitation in either the ED or the prehospital setting.

Review articles, letters to the editor, and individual case reports were not included. We excluded studies in which ketamine was used for procedural sedation, pain management, or as a component of rapid sequence intubation. We also specifically excluded studies where the reason for sedation was trauma or another known medical indication. The research methodology was submitted to Prospero (National Institute for Health Research, National Health Service, UK; https://www.crd.york.ac.uk/prospero, ID: 77135). Data were extracted by SLM into

Table 1. Search Strategy

Database	Year of Onset	Search Date	Total Papers	Selected	Search Strategy
PubMed (National Center for Biotechnology Information, National Institutes for Health [NIH], Washington, DC)	1966	May 2018	233	17	(emerg* OR prehosp* OR ambulance) AND (ketamine) AND (delirium OR exds OR abd OR "acute behavioral disturbance" OR agitat*)
Cochrane Library (John Wiley & Sons, Hoboken, NJ)	1992	May 2018	18	0	Ketamine
Google Scholar (Google, Mountain View, CA)	n/a	Jan 2018	44	5	Ketamine AND (agitation OR exds OR delirium OR violent OR dangerous) AND (emergency OR prehospital)
Ovid EmBase (Ovid Technologies, New York, NY)	1947	Feb 2018	191	27	((ketamine.mp. OR ketamine/) AND ((exp emergency ward/) OR (exp emergency health service/) OR (prehospital.mp.)) AND ((agitation.mp. OR agitation/) OR (violence/OR violence.mp) OR ((violen$ OR agitat$).mp.) OR (delirium mp. OR delirium/) OR (delirious.mp)))
Cumulative Index of Nursing and Allied Health Literature (CINAHL) (EBSCO Information Services, Ipswitch, MA)	1937	Jan 2018	127	11	(((MH "Ketamine") OR "ketamine") AND ((agitat*) OR (agress*) OR (violen*) OR (disturb*) OR (danger*) OR (combat*) OR (delir*)) AND (((MH "Emergency Service") OR (MH "Emergency Patients") OR (MH "Emergency Medicine") OR (MH "Emergency Treatment") OR (MH "Emergency Care") OR (MH "Emergency Medical Services") OR (MH "Emergencies") OR (MH "Rapid Response Team")) OR ("emergency") OR (emergenc*)))
ClinicalTrials.gov (National Library of Medicine, Bethesda, MD)	2008	May 2018	64	0	Ketamine, completed studies with results
Networked Digital Library of Theses and Dissertations (NDLTD, Provo, UT)		May 2018	60	0	(ketamine) AND (emergency OR violent OR agitated OR excited OR delirium OR exds)
Open Access Thesis and Dissertation (https://oatd.org)	1969	May 2018	10	0	(ketamine) AND (emergency OR violent OR agitated OR excited OR delirium OR exds)
Open Gray (Institut de l'Information Scientifique et Technique, Vandoeuvre-lès-Nancy, France)	1980	Jan 2018	3	0	(ketamine) AND (emergency OR violent OR agitated OR excited OR delirium OR exds)
National Institutes of Health Research Portfolio Online Reporting Tools (NIH RePORT) (NIH, Bethesda, MD)	1985	May 2018	0	0	Ketamine
American Doctoral Dissertations (EBSCO Information Services, Ipswitch, MA)	1902	May 2018	41	0	Ketamine
Academic Search Premier (EBSCO Information Services, Ipswitch, MA)	1911	Feb 2018	n/a	n/a	n/a
Prospero (University of York, York, UK)	2011	May 2017	9	0	Ketamine, review completed, published
Open Thesis (https://openthesis.org)	2007	Jan 2018	376	0	(ketamine) AND (emergency OR violent OR agitated OR excited OR delirium OR exds)
Total references from original search			1176		

Databases were searched from the earliest available datum until the date of the search. Google Scholar uses Google's proprietary algorithm, and does not limit its data by publication date. The results from Academic Search Premier were automatically combined with CINAHL, and not reported separately. Search strategies vary from database to database based on the characteristics of the database itself. For example, Prospero, ADD, NIH RePORT, and ClinicalTrials.gov are relatively smaller databases, and only the keyword "ketamine" was used as a primary search, and the study titles were reviewed manually. After all primary sources were reviewed and duplicates removed, we reviewed the bibliographies of the selected papers to find any other relevant studies.

Google Docs Sheet (Google, Mountain View, CA). In cases where data of interest were missing, we reached out to original authors by e-mail to complete the data abstraction. The length of follow-up was determined by the authors of the original studies, typically from initial presentation to ED disposition.

Participants, Interventions, Comparisons and Outcomes

Participants. We included studies whose participants presented with undifferentiated agitation and were evaluated by emergency physicians or by paramedics and were given ketamine for sedation. By necessity, this includes many patients who were ultimately diagnosed with treatable pathology (such as hyperthyroidism or hypoglycemia), but who were so agitated at the time of presentation that situational control preceded a thorough diagnostic work-up.

Interventions. Interventions included intravenous or intramuscular ketamine.

Comparisons. In our review, there were very few comparators available. Some studies used antipsychotics and benzodiazepines, but most were observational studies.

Outcomes. Outcomes studied were: 1) time to sedation; 2) requirement for additional sedation; 3) need for intubation by Emergency Medical Services (EMS); 4) need for intubation for nonairway issues; 5) need for intubation in the ED; 6) vomiting; 7) hypertension; 8) emergence reactions; 9) hypoxia; 10) hypersalivation; 11) laryngospasm; 12) disposition; 13) discharge diagnosis; 14) demographics (age, sex).

Study Quality

Studies were evaluated by SLM using the Methodological Index for Non-Randomized Studies (MINORS), a validated 14-point scale that accounts for selection, outcome, and endpoints of nonrandomized studies (Table 2) (10,27,31–47).

Due to the lack of randomized controlled studies on this topic, a traditional meta-analysis could not be undertaken. There are many potential reasons why the best available evidence may come from observational reports instead of a randomized controlled study, including feasibility, affordability, safety, ethics, and others (52,53). El Dib et al. suggested the term "proportional meta-analysis" for the procedure of combining nonrandomized studies when randomized studies are unavailable (54). According to Murad et al., "Quantitative analysis of non-comparative series does not produce relative association measures such as [odds ratios] or relative risks but can provide estimates of prevalence or event rates in the form of a proportion" (55). In our study, we used a random-effects model to study proportions because we believe that the heterogeneity observed is more likely due to differences in the populations sampled than to sampling error.

Summary Measures

For each endpoint, the occurrence rate (pooled proportion) and 95% confidence interval were calculated. Not all of the papers included all of the listed endpoints; hence, the denominators for each measure are different. Papers lacking a majority of these data were excluded. Continuous variables were combined to calculate mean, standard deviation, and range. When standard deviation was not available, it was computed from interquartile ranges in the method of Hozo et al. (56). The risk of intubation from each study was calculated using a random-effects model and a Forest plot was generated. To assess for publication bias, a funnel plot was created using log-odds (logit) compared with the standard error of the mean. Both of these diagrams were constructed using R (Version 3.4.3; The R Project, Free Software Foundation, Boston, MA). The authors received no funding support for this review.

RESULTS

The combined searches yielded 1176 hits (Table 1), of which 1116 were excluded. The remaining 60 were culled for duplicate hits, and 32 unique information sources were identified, including 25 published articles and seven posters/abstracts that were presented at national meetings. No relevant clinical trial or thesis or dissertation was found. We did not deliberately exclude non-English language articles; however, none were found. Only one of the seven poster/abstracts contained sufficient information for inclusion in the qualitative summary. When the bibliographies of the 25 articles were reviewed, one additional published paper was identified. Personal communication with authors also revealed another paper. After review of all papers, 10 were excluded because they lacked sufficient information for analysis, leaving 18 papers for abstraction (Figure 1, Table 2).

Demographics and Clinical Settings in Which Ketamine was Administered

Data were abstracted from 18 studies reflecting 650 patient encounters. In four studies, the ketamine was given in the ED (n = 110); in three, it was given during air medical transport (AMT, n = 61); and in the remainder, it was administered by paramedics during EMS ground

Table 2. Evidentiary Table

Citation (First Author, Year)	n	Setting	Comments	MINORS
Burnett, 2012 (34)	13	EMS	Thirteen agitated patients were given 5 mg/kg ketamine IM for chemical restraint by paramedics. Patients were followed through their ED stay. All EMS records reviewed. One ED record missing. Paramedics received formal education on Excited Delirium Syndrome (ExDS). Richmond Agitation Sedation Scale (RASS) used to quantify sedation.	10
Burnett, 2015 (40)	49	EMS	Fifty-one consecutive agitated patients were given ketamine by EMS for chemical restraint. Two were excluded due to missing data. Of those, 29% were intubated during their ED stay. Higher doses of ketamine were associated with greater likelihood of admission.	13
Burnett, 2015 (48)	110	EMS	Retrospective chart review of 55 patients receiving prehospital ketamine compared with haloperidol for chemical restraint. On-scene time was similar between 2 groups (17.6 vs. 18.2 mins). This study did not have enough data to be included in the meta-analysis.	n/a
Cole, 2016 (10)	146	EMS	This was a 12-month prospective crossover study of urban EMS providers. During the first 6 months of the study, agitated patients were given 10 mg i.m. haloperidol. During the second 6 months, the drug was changed to 5 mg/kg i.m. ketamine. Ketamine patients were sedated much more quickly (5 vs. 17 min), however, complications were much more common in the ketamine group. Hypersalivation 38%; vomiting 9%; emergence 10%; intubation 39%.	14
Cole, 2018 (41)	49	EMS	A total of 158 patients were given prehospital ketamine for agitation. Of those, 56 were brought to the study hospital and 7 were excluded for technical reasons, leaving 49 for evaluation. Patients received an average of 4.9 mg/kg i.m. ketamine, resulting in sedation in 4.2 min. Fifty-seven percent of patients were intubated when they reached the ED. Of the 7 patients who required additional sedative after ketamine, all 7 were intubated when they reached the ED. One patient died of septic shock on hospital day 27, unlikely related to ketamine.	14
Gangathimmaiah, 2017 (32)	21	AMT	Intravenous ketamine was used to sedate 21 patients for air medical transport. Of these, 3 were intubated for persistent agitation, not due to an airway issue. One patient had transient hypoxia, which resolved. None had vomiting. Of the 9 patients who developed hypertension, 2 were treated. One had salivation, which resolved. Most patients were put on ketamine infusions lasting an average of 120 min.	11
Ho, 2013 (47)	2	EMS	Case series of 2 agitated, intoxicated patients who were sedated with prehospital ketamine. Both patients were intubated in the ED due to severe metabolic acidosis, not due to airway compromise. There were no adverse effects of ketamine reported.	7
Hollis, 2017 (42)	38	EMS	Observational study of 38 patients given prehospital ketamine for sedation of agitation. Of these, 7 were intubated in the ED, but authors believe that they would have been intubated for reasons other than ketamine.	9
Hopper, 2015 (35)	32	ED	Observational study of 32 ED visits (representing 27 unique patients) who received ketamine either i.m. or i.v. in the ED for agitation. No hypoxia or emergence noted. There were no intubations (e-mail from Mike Wilson to me, 12/13/2017)	8
Isbister, 2016 (36)	49	ED	Ketamine was used as a second-line agent in 49 agitated patients who had already failed treatment with two doses of 10 mg i.m. droperidol in the ED. Very few adverse effects. No intubations.	14
Iwanicki, 2014 (43)	35	EMS	Poster presentation at North American Congress of Clinical Toxicology, 2014. Retrospective study of 35 patients who received prehospital ketamine, with 32 of 35 having acute intoxication with various substances. Half of the intoxicated patients were intubated, but no mention is made of the other 3. There were no episodes of laryngospasm or emergence.	8
Keseg, 2015 (37)	35	EMS	Observational study of 35 patients who received prehospital ketamine for chemical restraint. Of those, 8 were intubated, although one of those was for head trauma.	10
Kowalski, 2017 (44)	5	ED	Case series of patients who received ketamine in the ED for agitation. No adverse events seen.	7
Le Cong, 2012 (49)	18	AMT	Intravenous ketamine was used to sedate 18 psychiatric patients during air medical transport. Ketamine doses were small and almost always in conjunction with benzodiazepine. No patients were intubated and no adverse drug-related outcomes were seen during the 72-h follow-up.	11

(*Continued*)

Table 2. Continued

Citation (First Author, Year)	n	Setting	Comments	MINORS
Le Cong, 2015 (27)	653	AMT	Retrospective review of air medical transport service prior to and after implementation of a ketamine protocol for mental health patients. In this 9-year study, the overall rate of intubation was 2.3%. This study was not included in the analysis because it did not include individual chart review and it is not clear what percentage of patients actually received ketamine.	n/a
Meleamed, 2007 (50)	5	Mil	Military study of 18 combative trauma patients. Of those, 5 got ketamine. This paper was not included in the analysis because the primary reason for administration of ketamine was trauma agitation, not purely behavioral agitation. In this series, there was significant comorbidity. Of the 5 who received ketamine, 1 had a traumatic brain injury, 2 were hypotensive, 1 was intubated, and 1 died.	n/a
Olives, 2016 (45)	135	EMS	Observational study of 135 cases where prehospital ketamine was given for agitation. Of those, 85 were intubated and 2 died. Four of the 85 intubations were undertaken by EMS; the remainder in the ED. Both patients who died had postmortem diagnoses unrelated to ketamine. Male gender and late-night arrival to the ED were independent predictors of intubation. Authors speculate this may be because resources to monitor patients are scarcer at night and that agitated men pose greater threat than women.	12
Parsch, 2017 (33)	22	AMT	Crossover study of implementation of a ketamine protocol for transport of agitated patients (mostly by air). Prior to protocol, 36% of patients were intubated. After protocol, only 7% were intubated. Ketamine was given mostly i.v., and all patients were premedicated with benzodiazepine or antipsychotic. Only patients enrolled after the protocol were used in the analysis.	10
Riddell, 2017 (46)	24	ED	Observational study where protocol allowed emergency physicians to choose among benzodiazepines, ketamine, and haloperidol for chemical restraint of agitated patients. Mean time to sedation was much less with ketamine (7 vs. 15 min). Two of 24 patients were intubated, but reasons are not given.	14
Scaggs, 2016 (38)	7	EMS	Case series of 7 patients given ketamine by EMS. There were no intubations and very few adverse effects.	9
Scheppke, 2014 (39)	52	EMS	Observational study of 52 patients given ketamine by EMS for agitated patients. Of these, only 2 were intubated by EMS. Hospital follow-up was not provided.	11
Svenson, 2007 (51)	40	AMT	Observational study of 40 patients who received ketamine in aeromedical transport. Indications for sedation included trauma, burns, cardiac, and other medical issues, but no preponderance of psychiatric patients. This study was not included in the analysis because sedation was given for many reasons other than agitation.	n/a

EMS = Emergency Medical Services (ground); IM = intramuscular; ED = emergency department; AMT = air medical transport; Mil = military; MINORS = Methodological Index for Non-Randomized Studies.
Setting indicates where the ketamine was administered.

transport (n = 479). Patients were predominantly male, 67.6% (95% CI: 60.9–74.2%), and had an average age of 33 years (range 14–86).

Dosage

When patient weight is available, ketamine dosing is shown as mg/kg. In the prehospital setting, the weight is often unknown, and only the total dose is reported. The mean dose of intramuscular (i.m.) ketamine was 315 mg (SD 52, range 30–630 mg), or 4.9 mg/kg (SD 2.4, range 1.0–7.4) (10,34–45,57). Mean i.v. bolus dosing was 150 mg (SD 46, range 30–400), or 0.94 mg/kg (SD 0.74, range 0.31–2.79) (27,32,33,35,37,42,46). Many patients undergoing air medical transport also received an infusion of ketamine at a rate of 0.5–1 mg/kg/h.

Effectiveness of Ketamine, Including Time to Adequate Sedation and Need for Rescue Sedation

Mean time from ketamine administration to sedation was 7.21 min (SD 4.89; range 2–500), with 68.5% (95% CI: 61.7%–75.3%) achieving sedation within 5 min (10,34,36,38,39,41,44,46).

Whereas most patients were adequately sedated with a single dose of ketamine, 24.4% (95% CI: 20.5–28.3%) of patients required further sedation with benzodiazepines, antipsychotics, or additional ketamine (10,27,34–38,41,43–47).

Adverse Effects

Side effects of ketamine were relatively common. Vomiting was seen in 5.3% (95% CI: 2.4–8.2%), hypertension

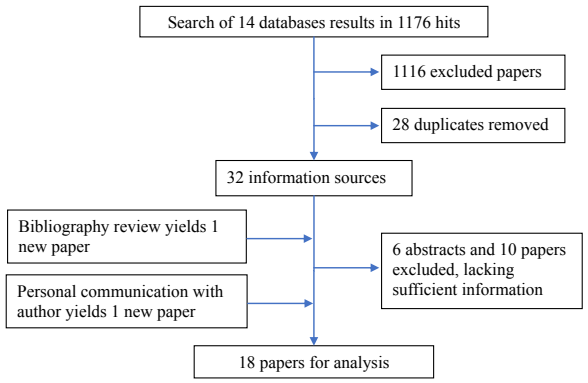


Figure 1. Database search methodology.

in 12.4% (95% CI: 5.8–18.9%), emergence delirium (also called recovery agitation) in 4.0% (95% CI: 1.3–6.7%), and transient hypoxia in 1.8% (95% CI: 0.1–3.6%). In these cases, the side effects were treated with reassurance or with additional medication. Laryngospasm was seen in 1.3% (95% CI: 0.3–2.3%), was usually transient, and was most commonly treated with bag-valve-mask ventilation. Hypersalivation was fairly common in 19.0% (95% CI: 13.1–25.0%) and was usually treated with suctioning. Antimuscarinic drugs (atropine, glycopyrrolate) were rarely used (Table 3).

Endotracheal Intubation

Overall, 197 of 645 patients required intubation after receiving ketamine, representing 30.5% (95% CI: 27.0–34.1%) of the total cohort. The indications for intubation were not always related to ketamine. Other reported reasons included cardiac arrest, head injury, and continued agitation. In 24.7% (95% CI: 21.3–28.2%) of patients, the reason for intubation was given as airway protection. The likelihood of eventual intubation is strongly correlated with the setting in which the ketamine is administered. Among patients who received ketamine by ground transport, 40.4% (95% CI: 36.0–44.8%) were intubated either in the field or upon arrival to the ED. In the cohort of patients who received ketamine for air medical transport, the intubation rate was 4.9% (95% CI: 0.0–10.3%). Patients who were given ketamine in the ED were intubated 1.8% (95% CI: 0.0–4.4%) of the time. The difference in intubation rates was compared using chi-squared test and was found to be statistically significant ($p < 0.00001$) (Table 4).

Table 3. Ketamine Side Effects

Observation	Number	Percent (95% CI)
Laryngospasm	6/463	1.3% (0.3–2.3%)
Hypoxia (not intubated)	4/220	1.8% (0.1–3.6%)
Vomiting	12/230	5.2% (2.3–8.1%)
Emergence	10/286	3.5% (1.4–5.6%)
Hypertension	12/99	12.1% (5.7–18.6%)
Hypersalivation	32/170	18.8% (12.9–24.7%)
Required additional sedation	114/467	24.4% (20.5–28.3%)

CI = confidence interval.
Note that not all studies reported each side effect.

Diagnoses and Disposition

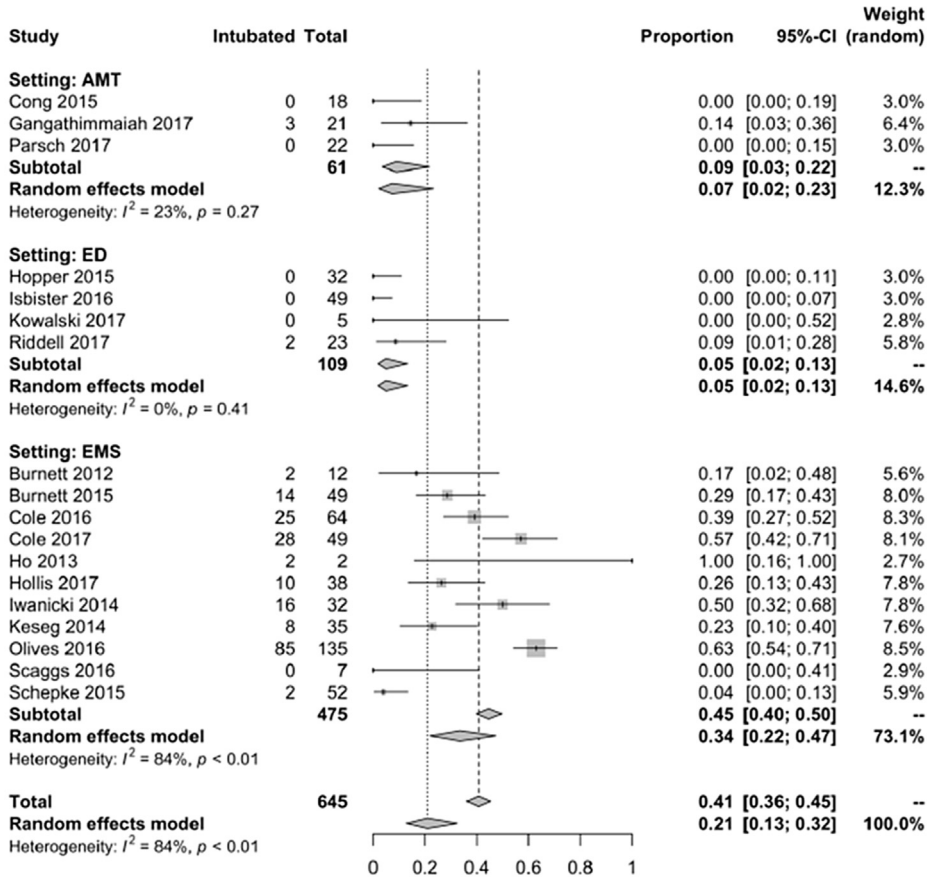
When ED disposition was available, roughly half the patients who were given ketamine were admitted to a medical floor or intensive care unit. The remainder was evenly split between psychiatric admissions and discharges to home. When a final diagnosis was available, the majority of patients had psychiatric diagnoses with or without substance abuse. Less than 10% ultimately had a medical diagnosis (Table 5).

DISCUSSION

Administration of ketamine is highly associated with intubation, far more than other sedative agents. Cole et al. compared prehospital ketamine with haloperidol, and found the intubation rate was 39% for ketamine vs. 4% for haloperidol (10). In another study, presented as an abstract, Hibbs et al. showed that patients were more likely to be intubated when they were sedated with ketamine in the ED than with olanzapine (4% vs. 0%) (58). However, in one study on air-medical transport, a ketamine sedation protocol reduced the likelihood of in-flight intubation from 3.5% prior to the protocol to 2.3% afterwards (27).

Existing literature does not completely characterize these heterogeneous agitated patients, however, a review of the final discharge diagnoses of patients given prehospital ketamine for agitation reveals traumatic intracranial hemorrhage, penetrating trauma of the head and neck, septic shock, and profound metabolic derangements; all patients were appropriately intubated. The differences observed in intubation rates based on their environments (AMT, EMS, ED) may, in fact, be differences in the patients themselves. Patients in the ED, or awaiting AMT for a psychiatric illness, have already tolerated transport to the ED and, in many cases, establishment of i.v. access or several doses of other sedatives. When comparing and contrasting these patients with acutely undifferentiated, intoxicated, violent patients engaged with the general public or law enforcement, it is not surprising that their final diagnoses, and as such, the percentage needing intubation, vary. Regardless of the reason, when EMS transports a dissociated patient who only moments ago was agitated, aggressive, and violent in the field and is now unresponsive, many emergency physicians will opt for intubation.

Table 4. Intubation Rates Among Patients Given Ketamine for Agitation



CI = confidence interval; AMT = air medical transport; ED = emergency department; EMS = Emergency Medical Services (prehospital).

Dosing

In general, i.v. ketamine provides the most reliable and fastest onset of action, but establishing an i.v. line in an agitated patient can be challenging. Some have recommended the intranasal route as being safer, as it avoids using sharps (59).

Some authors have posited that higher doses of ketamine are associated with an increased frequency of intubation (35,40,60). Whereas sedative-hypnotics and opioids clearly have a dose–response relationship with respiratory depression, published pharmacologic literature suggests this is not the case for ketamine. Ketamine causes sedation by inducing dissociation (a state of disconnection from the outside world with preserved respiratory reflexes) via disconnection of the thalamocortical and limbic systems (18). Dissociation does not seem to be dose related, rather, it is a threshold effect that is either present or absent (26). Once dissociated, a patient cannot be "more dissociated." This existing literature, however, examines predominantly patients undergoing anesthesia or procedural sedation, and not the patients with undifferentiated agitation in our review. Literature on agitated patients is mixed; Burnett et al. reported a retrospective analysis of agitated patients who were intubated and received a mean dose of 6.2 mg/kg of i.m. ketamine (n = 14), compared with 4.9 mg/kg for those not intubated (n = 35) (40). Subsequent prospective literature on similar patients found no relationship between ketamine dose and intubation (41,45). As no randomized trials have been conducted, this question remains unanswered and should be the subject of more rigorous research in the

Table 5. Diagnosis and Disposition of Patients Receiving Ketamine

	Number	Mean (95% CI)
Diagnosis (n = 151)		
Psychiatric	77	51.0% (43.0–59.0%)
Substance abuse	61	40.4% (32.6–48.2%)
Medical	13	8.6% (4.1–13.1%)
Disposition (n = 209)		
Home/jail/outpatient facility	48	23.0% (17.3–28.7%)
Psychiatric inpatient	48	23.0% (17.3–28.7%)
Medical inpatient	113	54.1% (47.3–60.8%)

CI = confidence interval.

future so these vulnerable, critical patients may receive the lowest effective dose of ketamine.

Finally, publication bias may favor studies that demonstrate safety of ketamine use. As recently as 2017, ketamine has been described as a "novel agent" and a "key cog" for treatment of agitated delirium (44,56). In our review, 6 of 18 studies showed zero episodes of intubation related to ketamine (27,33,35,36,38,44). A funnel plot shows that only 8 of 18 studies fall within the 95% confidence interval. The shifts are fairly balanced, with five small studies shifted to the left and three larger studies to the right. This argues against a publication bias favoring ketamine (Figure 2).

Limitations

Several limitations should be considered when interpreting the results of this study. First, the overall quality of data from all studies is poor. All studies were observational; the majority were retrospective, and some were simply case series. No randomized or blinded trials have been published; such studies are needed to better define the role and side-effect profile of ketamine for agitation.

Second, there likely exists an outcome difference between i.m. and i.v. ketamine. Whereas EMS and ED literature tend to favor i.m. ketamine, AMT literature usually describes i.v. ketamine. Moreover, some papers do not clearly separate patients by route of administration. In addition, many prehospital studies do not include patient weights, making an accurate mg/kg dose calculation impossible. The variation in dosage and routes among studies makes it difficult to draw firm conclusions on the effect of dose on important parameters such as time to sedation and intubation.

Third, our analysis combines data from several heterogeneous settings. For example, one of our measured outcomes was control of agitation. Some studies used a formal agitation grading system, whereas others simply used a summary statement that the agitation was controlled (10,41). The definition of "controlled" will necessarily vary by setting. Violent behaviors that are tolerated in an ED may be completely unacceptable in a moving ambulance or, much less, small aircraft. Furthermore, patients with agitation in the ED, AMT, or ground EMS may have different risk profiles for critical illness. Patients from the general public transported by ground EMS tend to be far more undifferentiated, and as such, may have a much different risk profile.

Fourth, both study settings and the patients themselves may be heterogeneous. As an example, the largest study on ketamine administered in the ED reported the mean time to sedation was 20 min, even after two doses of

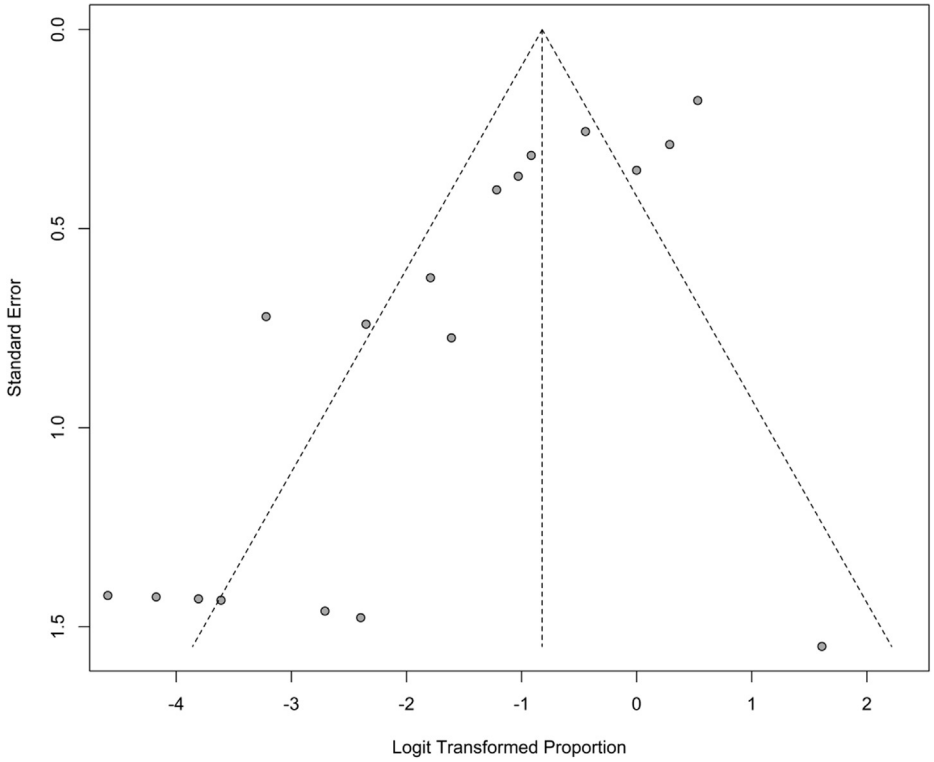


Figure 2. Funnel plot. Eight of 18 studies fall outside the "funnel" of the 95% confidence interval. Of those, five smaller studies (with greater standard error) demonstrate lower incidence of intubation. The three studies that show higher rates of intubation included more patients and have smaller standard errors. Taken together, this argues against publication bias.

10 mg droperidol were unsuccessful (36). This is approximately three times as long as the next lowest study (7 min) and 10 times as long as the lowest study (1.8 min) (38,44). It is possible that this group of droperidol-resistant patients are also relatively ketamine-resistant as well due to co-ingestion of other stimulants, and are therefore not representative of the population as a whole. Comparing the use of ketamine as a primary therapy, as opposed to a rescue therapy after multiple doses of antipsychotics, may make interpreting the available data more difficult.

Fifth, our data set may be subject to reporting bias; studies reporting only prehospital (and not ED) data are very likely to miss intubations and adverse respiratory events, as the majority of intubations associated with ketamine are performed on patients who received ketamine by ground EMS providers and were intubated only when they reached the ED.

Sixth, no studies are available to assess the effect of ketamine on psychiatric outcomes for this patient population. As volunteer studies of patients with schizophrenia receiving ketamine have demonstrated, ketamine may worsen hallucinations (23,24). If ketamine has a substantially negative impact on the psychiatric outcomes of these patients, it may limit its feasibility in the future. Further study of psychiatric outcomes in these patients is warranted.

Last, comparative data with other sedatives are lacking. Currently, only two studies assessed the effectiveness of ketamine compared with other sedatives; one small study in the ED that was observational in nature, where physicians selected their agent of choice, and one in the prehospital environment that observed the natural change of an EMS protocol from haloperidol to ketamine (10,57). Although both studies suggest ketamine has a more rapid onset of action compared with other agents such as haloperidol or benzodiazepines, both studies suffer from significant selection bias and lack of blinding. Riddell et al. studied a convenience sample of 24 patients where the treating physician specifically chose ketamine for the patient, whereas Cole et al. only studied 64 patients treated with prehospital ketamine brought to a single ED in an observational study of a before/after protocol change. Neither study was blinded (10,46). Furthermore, time to adequate sedation may not be the optimal primary outcome measure. In patients with ExDS, rapid sedation is critical to prevent the metabolic derangements and subsequent associated mortality, however, in the vast majority of agitated patients, the safety and side-effect profile of the agent, such as incidence of respiratory depression, partial dissociation, or extrapyramidal effects, is equally important. Blinded, randomized trials are needed to properly assess the effectiveness of ketamine as well as its true side-effect profile and proclivity to cause respiratory depression.

CONCLUSIONS

Ketamine seems to provide rapid sedation for the control of agitated patients. This efficiency must be weighed against the strong association with endotracheal intubation, which is far more common when used by EMS for ground transportation in contrast to ketamine used for agitation in the ED or for air medical transport. Other side effects, such as vomiting, hypersalivation, emergence phenomena, and respiratory depression are common, and as such, the emergency physician should be prepared to immediately manage them.

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ARTICLE SUMMARY

1. Why is this topic important?

Rapid tranquilization of agitated patients can prevent injuries. The combination of benzodiazepines and antipsychotics have many drawbacks, and ketamine may be a better choice.

2. What does this review attempt to show?

This review attempts to describe the safety and efficacy of ketamine in agitated patients in the prehospital and emergency department (ED) setting.

3. What are the key findings?

Ketamine provides an effective and rapid method for the control of agitated patients. Ketamine is strongly associated with endotracheal intubation when given by prehospital personnel, but not when given in the ED. Most other side effects of ketamine are minor.

4. How is patient care impacted?

Physicians who use traditional methods of sedating agitated patients should consider ketamine as an alternative, considering its relative safety when used in the ED. Similarly, prehospital providers should understand that using ketamine for sedation may result in intubation when the patient arrives in the ED.