Premedication With Midazolam or Haloperidol to Prevent Recovery Agitation in Adults Undergoing Procedural Sedation With Ketamine: A Randomized Double-Blind Clinical Trial

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Study objective: We evaluate the effect of midazolam and haloperidol premedication for reducing ketamine-induced recovery agitation in adult patients undergoing procedural sedation. We also compare physician satisfaction and recovery time.

Methods: We randomized emergency department patients older than 18 years who needed procedural sedation to receive 1 of the following 3 interventions in double-blind fashion 5 minutes before receiving intravenous ketamine at 1 mg/kg: intravenous distilled water, intravenous midazolam at 0.05 mg/kg, or intravenous haloperidol at 5 mg. Our main study outcomes were recovery agitation as assessed by the maximum observed Pittsburgh Agitation Scale score and by the Richmond Agitation-Sedation Scale score at 5, 15, and 30 minutes after ketamine administration. Our secondary outcomes were clinician satisfaction and recovery duration.

Results: We enrolled 185 subjects. The maximum Pittsburgh Agitation Scale score was significantly less with midazolam compared with placebo (difference 3; 95% confidence interval 1.27 to 4.72) and with haloperidol compared with placebo (difference 3; 95% confidence interval 1.25 to 4.75), and Richmond Agitation-Sedation Scale scores at 5, 15, and 30 minutes trended lower with the active agents. Midazolam and haloperidol significantly delayed recovery but did not alter overall clinician satisfaction.

Conclusion: For adult procedural sedation, premedication with either midazolam 0.05 mg/kg or haloperidol 5 mg intravenously significantly reduces ketamine-induced recovery agitation while delaying recovery. [Ann Emerg Med. 2019;73:462-469.]

Please see page 463 for the Editor's Capsule Summary of this article.

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INTRODUCTION

Background

Emergency department (ED) patients frequently require painful procedures, and ketamine is a safe and effective agent widely used for this purpose, particularly in children. Some emergency physicians are reluctant to use ketamine in adults because of concern in regard to more frequent recovery agitation.

Coadministration of other drugs has been proposed, especially the benzodiazepines, to reduce recovery agitation. Coppel et al[1] first described that coadministration of diazepam appeared to reduce recovery agitation (so-called emergence phenomenon) of ketamine in adults. However, there was no agreement on the definition of recovery agitation and delirium, and later studies could not provide convincing similar results.[2-6] In a randomized trial, Sener et al[7] showed that midazolam can effectively reduce ketamine-induced agitation in adult patients. There are also studies that have proposed that haloperidol can reduce the incidence of ketamine-induced agitation.[8,9]

Importance

If coadministered agents can diminish recovery agitation with ketamine in adults, then their use might become common or routine.

Goals of This Investigation

The goal of our study was to evaluate the effect of midazolam and haloperidol premedication on ketamine-induced recovery agitation 5, 10, and 15 minutes after administration, and maximal recovery agitation. Our

Editor's Capsule Summary

What is already known on this topic

Emergency physicians are often reluctant to sedate adults with ketamine, fearing unpleasant hallucinatory recovery reactions.

What question this study addressed

Does premedication with midazolam or haloperidol decrease recovery agitation after adult ketamine sedation?

What this study adds to our knowledge

In this 3-arm randomized controlled trial of 185 subjects, prophylactic midazolam and haloperidol were associated with significantly lower recovery agitation scores and a decreased frequency of clinically important recovery agitation. Recovery times were also longer with these adjuncts (median 17 and 32 additional minutes, respectively).

How this is relevant to clinical practice

Midazolam at 0.05 mg/kg intravenously or haloperidol at 5 mg intravenously before medication reduces the magnitude of recovery agitation after emergency department ketamine sedation in adults while modestly extending recovery time.

secondary objectives were to compare physician satisfaction between groups and recovery time.

MATERIALS AND METHODS

Study Design

This was a randomized, double-blind, placebo-controlled, multiarm trial. The study was approved by the university ethics committee.

Setting and Selection of Participants

We enrolled adults (>18 years) who needed procedural sedation in the ED of Sina Hospital (annual ED census 35,000), identified during the shifts when one of the researchers was present. We excluded individuals with any contraindication to ketamine, midazolam, or haloperidol (Figure 1). Written informed consent was obtained.

Interventions

We randomized subjects into 3 groups, using permuted blocks with a varying length of 3 to 9. Every morning, a person not involved in the study or patient care prepared and numbered several study packages and stored them in a locked drawer. When each new subject was enrolled by an attending emergency physician, he or she was allocated to the next number according to the randomization schedule. The physician then picked up the matched, numbered package from the drawer. The patient and clinical caregivers were thus blinded to study group.

Each study package contained 2 blinded syringes of premedicants or placebo and a third nonblinded syringe containing ketamine at 50 mg/mL. Premedicants were a 2-mL syringe containing 1 mL of either distilled water placebo or haloperidol (5 mg/mL) and a 10-mL syringe containing distilled water or midazolam at 1 mg/mL (10 mg). The patients thus received the following in blinded fashion: placebo arm subjects received intravenous injections of distilled water (1 mL to simulate haloperidol and then 0.05 mL/kg to simulate midazolam), haloperidol arm subjects received 1 mL (5 mg) of haloperidol and then distilled water at 0.05 mL/kg, and midazolam arm subjects received 1 mL of distilled water and midazolam at 0.05 mL/kg (0.05 mg/kg). Five minutes after the premedication, each patient received intravenous ketamine at 1 mg/kg, administered during 60 seconds.

Before sedation, we recorded for each subject the baseline values of pulse rate, blood pressure, respiratory rate, and oxygen saturation, and obtained an ECG. During sedation, all patients received supplemental oxygen by nasal cannula (5 L/min) and were continuously monitored by 3-lead ECG, pulse rate, respiratory rate, and oxygen saturation. Blood pressure was recorded every 5 minutes by an automatic blood pressure monitor.

Outcome Measures

Our main study outcomes were recovery agitation as assessed by the Richmond Agitation-Sedation Scale score at 5, 15, and 30 minutes after ketamine administration, and the maximum observed Pittsburgh Agitation Scale score. Our secondary outcomes were clinician satisfaction and recovery duration.

Data Collection and Processing

Physician investigators assessed the Richmond Agitation-Sedation Scale score[10] at 5, 15, and 30 minutes after ketamine injection. The scale has 10 levels, with 4 levels of anxiety and agitation (1 to 4, which indicates combative), 1 level that describes calm and alert (0), and 5 levels of sedation (–1 to –5, which indicates unarousable). The values and definition of each level and the instructions for assessment are shown in Table E1 (available online at http://www.annemergmed.com).[10,11]

<18 y	Moderate to severe dementia, as documented by medical history
Pregnancy	History of Parkinson's disease
History of significant cardiovascular disease, CHF class 3, 4	History of structural brain damage
History of central nervous system lesions or injuries, increased ICP	Corrected QTc interval >500 ms in previous records or on current ECG
History of ocular pathology, increased IOP	History of drug use with prolonged QT interval
History of thyroid disease	History of torsades de pointes
Acute pulmonary infections according to patient's history and physical examination results	History of neuroleptic malignant syndrome
	Family history of dystonic reactions to drugs
Conditions requiring stimulation of the posterior pharynx	Epilepsy or history of seizures
Ingested solid food in the previous 4 h or clear liquids in the previous 2 h	Chronic psychiatric disease
History of acute intermittent porphyria	Intoxication based on patient's symptoms and physical examination results
History of alcoholism	
History of hepatic impairment	History of bone marrow suppression
History of myasthenia gravis	Allergy to haloperidol, ketamine, or midazolam as established by direct questioning and available medical history
Respiratory depression (RR <10, cyanosis, or pulse oximeter oxygen saturation <90%)	

Figure 1. Exclusion criteria. *CHF*, Congestive heart failure; *ICP*, intracranial pressure; *IOP*, intraocular pressure.

Physician investigators assessed the maximal Pittsburgh Agitation Scale score during sedation and recovery. The scale (Appendix E1, available online at http://www.annemergmed.com) rates the severity of agitation in 4 general behavior groups: aberrant vocalization, motor agitation, aggressiveness, and resistance to care, each on a scale ranging from 0 to 4. The total score of agitation is the summation of these 4 dimensions, ranging from 0 to 16.[12]

Patients who have a Pittsburgh Agitation Scale score of 3 or greater in any dimension have disruptive behaviors, and we defined this threshold as clinically important recovery agitation for our study.

We evaluated physician satisfaction with the sedation procedure with the Clinician Satisfaction With Sedation Instrument, which is a 21-item questionnaire in which response options are presented on a 7-point Likert scale (Table E2, available online at http://www.annemergmed.com). The questions are divided into 3 subscales, including satisfaction with sedation administration, satisfaction with recovery, and overall satisfaction.[13]

We defined recovery time as the time from administration of the first syringe to the time at which the patient was alert and awake or easily aroused by minimal stimulation.

Primary Data Analysis

In accordance with a previous study,[7] we calculated our sample size assuming an agitation incidence of 25% in the group receiving ketamine alone and 5% in the premedicated groups. Using statistical targets of $\alpha<.05$ and 80% power, we required a minimum of 59 patients in each of the 3 groups (total of 177). To compensate for loss to follow-up, we enrolled 62 patients in each group.[7]

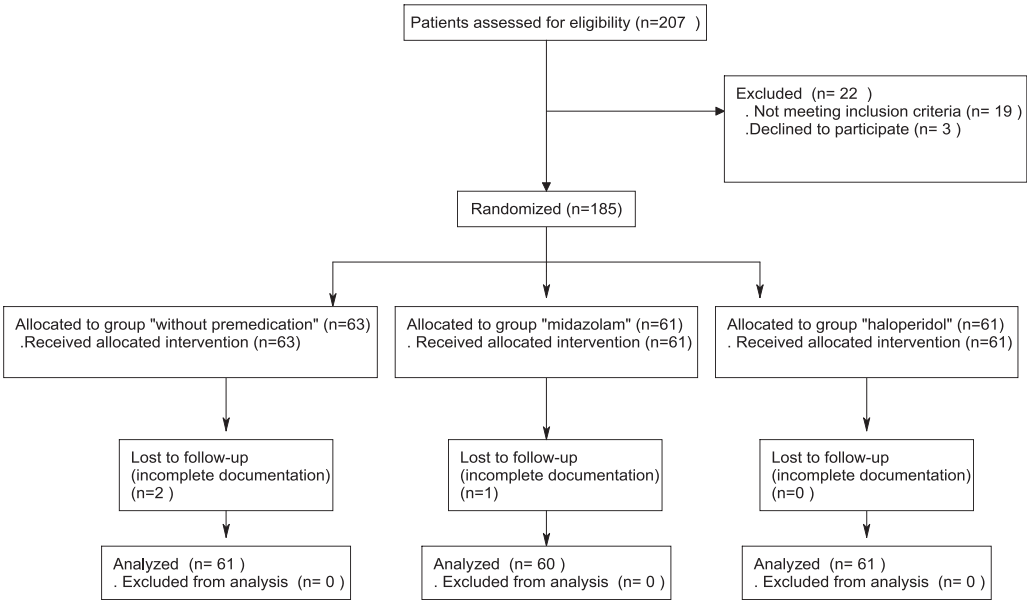

Figure 2. Flow of study subjects.

Table 1. Baseline characteristics of study subjects.

	Total		Groups		
Parameter	**Mean (SD)**	**Median (IQR)**	**Placebo, Median (Range*)**	**Midazolam, Median (Range*)**	**Haloperidol, Median (Range*)**
Age, y	37.5 (12.00)	36 (19–65)	38 (19–65)	36.5 (19–61)	35 (20–63)
Weight, kg	76.5 (8.91)	76 (57–98)	75 (60–94)	79 (58–98)	76 (57–95)
Sex, male, No. (%)	—†	165 (90.7)	56 (91.8)	52 (86.7)	57 (93.4)
Procedure, No. (%)					
Upper extremity fracture	—	45 (24.7)	14 (23.0)	12 (20.0)	19 (31.1)
Lower extremity fracture	—	69 (37.9)	17 (27.9)	25 (41.7)	27 (44.3)
Shoulder dislocation	—	45 (24.7)	17 (27.9)	16 (26.7)	12 (19.7)
Other‡	—	23 (12.6)	13 (21.3)	7 (11.7)	3 (4.9)

IQR, Interquartile range.
*Range: interval between minimum and maximum.
†Dashes indicate not applicable.
‡Complex laceration repair (mostly on face or genitalia), abscess incision, nasal fracture closed reduction, mandibular fracture stabilization.

For data description, median, interquartile range, frequency, and percentage are reported. Ninety-five percent confidence intervals for difference in medians of ordinal outcomes were estimated for all pairs of treatment groups, using 1,000 bootstrap replications with sample size equal to the original sample size of approximately 60 subjects in each treatment group.

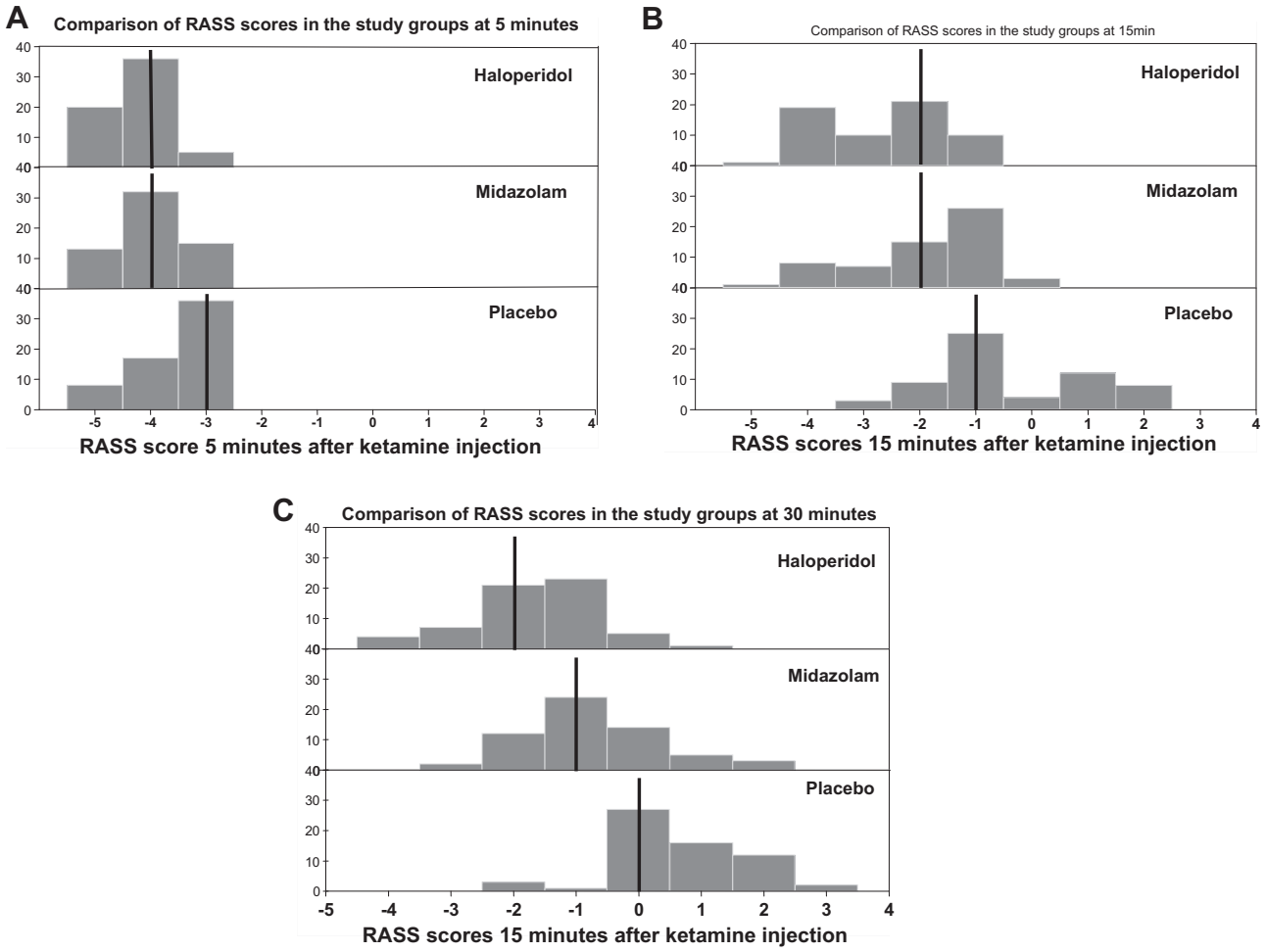

Figure 3. The distributions of Richmond Agitation-Sedation Scale scores.

All statistical analysis was conducted with SPSS (version 24; IBM Corp, Armonk, NY) and Stata Statistical Software (version 15; StataCorp, College Station, TX).

RESULTS

Characteristics of Study Subjects

We enrolled 185 subjects in the study from July 2016 to March 2017 (Figure 2). Baseline clinical characteristics and demographic features were similar between the groups (Table 1).

Main Results

The distributions of Richmond Agitation-Sedation Scale scores are shown in Figure 3. The distributions of total Pittsburgh Agitation Scale scores and scores in each behavioral dimension are shown in Figure 4. Differences in study outcomes and their sizes of effect are shown in Table 2.

The incidence of ketamine-induced agitation (maximal total Pittsburgh Agitation Scale score >0) was 63.9% in the group who received no premedication (the control group), 25% in the group who received midazolam as premedication (relative risk reduction 60.9%), and 19.7% in the group who received haloperidol as premedication (relative risk reduction 69.2%).

The recovery time was significantly longer in the midazolam and haloperidol groups (Table 2).

Figure E1 (available online at http://www.annemergmed.com) presents the details of clinician satisfaction and a scatter plot of agitation score versus physician satisfaction score. The overall clinician satisfaction with the sedation was not significantly different between the 3 study groups. However, as shown, satisfaction with the rapidity of recovery, effect of sedation on the procedure, patient's ability to communicate, retaining postoperative information, and postoperative adverse effects was significantly different between groups.

Appendix E2 (available online at http://www.annemergmed.com) displays the correlation between the total scores of the Pittsburgh Agitation Scale and Richmond Agitation-Sedation Scale at 5, 15, and 30 minutes (r=0.366, r=0.537, and r=0.534, respectively) and shows consistency between these 2 scoring systems for agitation in this study.

Other measured adverse events are presented in Table 3.

LIMITATIONS

There was a preponderance of male patients (90%) in our study because of the greater number of them visiting our ED who needed procedural sedation. This disproportionate distribution of patients' sex did not allow us to conduct robust comparison of outcomes between male and female patients.

We recruited our data from patients who needed procedural sedation in the crowded ED of a big trauma center, in which most of the patients' injuries were due to fighting or accidents. These kinds of populations may have

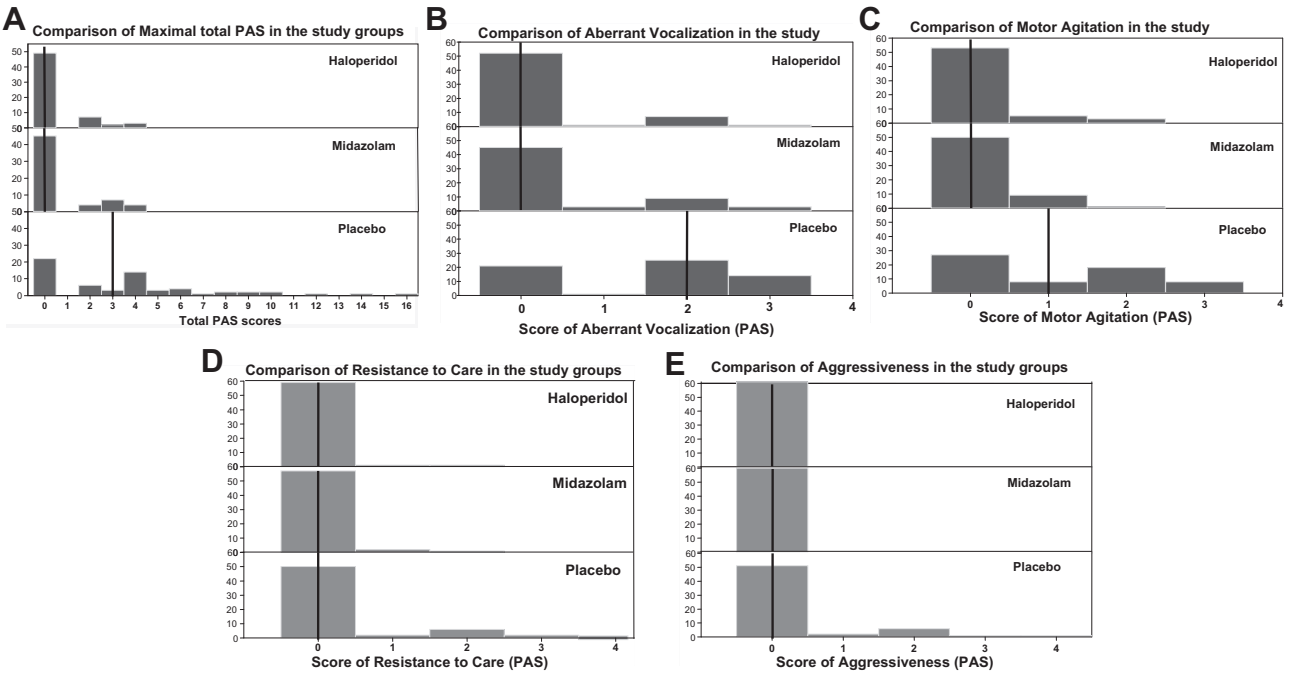

Figure 4. The distributions of Pittsburgh Agitation Scale (PAS) scores.

Table 2. Summary of outcomes and differences between groups.

Parameter	Groups			Difference (95% CI)*		
	Placebo, Median (IQR)	Midazolam, Median (IQR)	Haloperidol, Median (IQR)	Placebo vs Midazolam	Placebo vs Haloperidol	Midazolam vs Haloperidol
RASS, min						
5	−3 (−4 to −3)	−4 (−4 to −3.5)	−4 (−5 to −4)	1 (0.53 to 1.47)	1 (0.48 to 1.52)	0.05 (−0.1 to 0.1)
15	−1 (−1 to 1)	−2 (−3 to −1)	−2 (−4 to −2)	1 (−0.08 to 2.08)	1 (−0.05 to 2.05)	0 (−1.36 to 1.36)
30	0 (0 to 1)	−1 (−1 to 0)	−2 (−2 to −1)	1 (0.04 to 1.96)	2 (0.71 to 3.29)	1 (0.06 to 1.94)
Total PAS score	3 (0 to 5)	0 (0 to 1)	0 (0 to 0)	3 (1.27 to 4.72)	3 (1.25 to 4.75)	0 (NA†)
Aberrant vocalization	2 (0 to 2)	0 (0 to 0.5)	0 (0 to 0)	2 (1.61 to 2.39)	2 (1.69 to 2.31)	0 (NA†)
Motor agitation	1 (0 to 2)	0 (0 to 0)	0 (0 to 0)	1 (−0.03 to 2.03)	1 (−0.06 to 2.06)	0 (NA†)
Aggressiveness	0 (0 to 0)	0 (0 to 0)	0 (0 to 0)	0 (NA†)	0 (NA†)	0 (NA†)
Resistance to care	0 (0 to 0)	0 (0 to 0)	0 (0 to 0)	0 (NA†)	0 (NA†)	0 (NA†)
Agitation incidence,‡ No. (%)	39 (63.9)	15 (25.0)	12 (19.7)	38.9 (22.6 to 55.2)	44.3 (28.6 to 59.9)	5.3 (−9.5 to 20.1)
Clinically important recovery agitation§ No. (%)	16 (26.2)	3 (5.0)	1 (1.6)	21.2 (8.9 to 33.6)	24.6 (13.1 to 36.1)	3.4 (−3.0 to 9.7)
Clinician satisfaction‖	98 (88 to 107)	101 (97 to 104.5)	97 (94 to 100)	−3 (−9.12 to 3.12)	1 (−4.91 to 6.91)	4 (1.57 to 6.43)
Recovery time, min	18 (15 to 25)	35 (30 to 42.5)	50 (40 to 60)	−17 (−24.95 to −9.05)	−32 (−38.81 to −25.19)	−15 (−23.01 to −6.99)

CI, Confidence interval; *RASS*, Richmond Agitation Sedation Scale; *NA*, not available.
Results are presented as median (IQR) or frequency (%).
*The 95% CI for difference in medians, using bootstrap with 1,000 replications.
†The estimated variance based on bootstrap samples almost equal to zero. 95% CIs for difference in medians were narrow and very close to the point estimate.
‡Agitation incidence was defined as the proportion of the patients with total PAS score >0. All 2-way 95% CIs for the difference of agitation incidence for treatment groups were calculated with a 2-proportion comparison method.
§Clinically important recovery agitation was defined as the proportion of patients with a score of at least 3 in any behavioral dimension of PAS. All 2-way 95% CIs for the difference of agitation incidence for treatment groups were calculated with a 2-proportion comparison method.
‖Calculated with the Clinician Satisfaction With Sedation Instrument.

a greater tendency for agitation, and this could have affected our results and may explain the substantial incidence of ketamine-induced agitation in our sample. However, we excluded patients with any history of psychiatric problems to prevent this kind of bias. Nevertheless, multicentric studies could solve this problem with more validity.

Discrepant definitions and various standardized rating scales for measuring agitation prevented us from directly comparing our results with those of previous studies.

DISCUSSION

In this randomized, double-blind, placebo-controlled, multiarm trial, we found that premedication of ketamine with either midazolam or haloperidol could reduce the incidence and severity of ketamine-induced agitation.

The incidence of ketamine-induced agitation in our study (63.9%) was much higher than that in previous studies. However, the incidence of disruptive behaviors that was clinically important (a score of at least 3 in any behavioral dimension of the Pittsburgh Agitation Scale) was 26.2%. The incidence of ketamine-induced agitation has been estimated to be approximately 15% to 20% in some of the studies performed in Europe and America[1,5,14,15] and approximately 25% and 30% in Turkey and India, respectively.[6,7] In a narrative review, Strayer and Nelson[16] stated that psychiatric adverse events are reported in 0% to 76% of patients emerging from ketamine sedation. This discrepancy could originate from genetic, environmental, or cultural differences between populations. However, this broad range of the incidence of ketamine-induced agitation could be accounted for by inconsistencies in classification, measurement, and definitions for agitation. In many previous studies, it is not clear which symptoms were identified as agitation. Some studies assigned recovery agitation according to the patient's dreams and experiences, or observations that researchers made during the sedation and recovery, none of which are objective.[2,4-7,9,14,17,18] Other researchers used a visual analog scale scored by

Table 3. Adverse events.

Adverse Events	Groups (Premedications), No. (%)		
	Placebo, N=61	Midazolam, N=60	Haloperidol, N=61
Nausea	3 (4.9)	3 (5)	2 (3.2)
Vomiting	2 (3.2)	0	0
Cardiovascular events	0	0	0
Change in blood pressure	0	0	0
Laryngospasm	0	0	0
Apnea	0	0	0
Hypoxia	0	0	0
Severe agitation (PAS score >8) (treated with midazolam)	6 (9.8)	0	0

patients or clinicians to detect agitation.[19] There was only one study, performed by Trivedi et al,[20] in which an actual delirium assessment scale was used to detect recovery agitation.

In our study, we used a valid scoring system to detect agitation related to sedation. Using a highly sensitive method to detect agitation may be a reason for the higher incidence of recovery agitation in our study. Meanwhile, we assessed clinically important agitation and clinician satisfaction to determine agitation's importance.

We detected a substantial reduction in recovery agitation incidence and severity in the group of patients who were premedicated by midazolam. This finding is compatible with those of the majority of previous studies that assessed the effect of benzodiazepines for the reduction of ketamine-induced agitation.[2,4,7,14,15,21] In a similar way, premedication by haloperidol significantly reduced recovery agitation incidence and severity. Although to our knowledge there are no qualified clinical trials or even large sample case series about premedication of ketamine by haloperidol in adult patients, data from animal studies and also studies that have been performed with children have the same trend as our results.[9,16,22]

We also evaluated clinician satisfaction with sedation, which was not significantly different in the 3 arms of the study. However, satisfaction with different aspects of the procedure was studied and recognized to be distinct. For example, the longer recovery time associated with premedication by haloperidol, and to a lesser extent midazolam, affected clinician satisfaction significantly.

In summary, in adult patients undergoing procedural sedation in the ED, premedication of ketamine by either midazolam or haloperidol significantly reduces ketamine-induced recovery agitation while delaying recovery.

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Author contributions: PP conceived the study. NA and PP designed the trial, supervised conduct of the trial and data collection, and drafted the article. NA, PP, and AA contributed to data collection. NA and MY provided statistical advice on study design and analyzed the data. AAA provided statistical advice on analysis and graphs. PP takes responsibility for the paper as a whole.

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IMAGES IN EMERGENCY MEDICINE

(continued from p. 452)

DIAGNOSIS:

Dilated cardiomyopathy complicated by left ventricular thrombus with systemic arterial embolism. CT angiography of the whole aorta demonstrated total occlusion of the infrarenal abdominal aorta to aortic bifurcation, along with the common iliac arteries and distal main renal artery leading to subtotal left renal infarction. Echocardiography confirmed the presence of a large left ventricular apical thrombus. The patient was treated with systemic heparinization and bilateral transfemoral thromboembolectomy and bilateral lower-leg fasciotomies. The patient was discharged home after 12 days with oral anticoagulation.

In patients with dilated cardiomyopathy, the incidence of left ventricular thrombus ranges from 13% to 50%.[1,2] Left ventricular thrombus is most often diagnosed with echocardiography, although cardiac magnetic resonance imaging has greater sensitivity.[3] Without systemic anticoagulation, the risk of arterial embolization has been estimated to be 29%.[4] Warfarin is the most commonly used anticoagulant therapy for left ventricular thrombus, but heparin-based approaches have also been described.[5]

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