Midazolam-Droperidol, Droperidol, or Olanzapine for Acute Agitation: A Randomized Clinical Trial

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Study objective: We aim to determine the most efficacious of 3 common medication regimens for the sedation of acutely agitated emergency department (ED) patients.

Methods: We undertook a randomized, controlled, double-blind, triple-dummy, clinical trial in 2 metropolitan EDs between October 2014 and August 2015. Patients aged 18 to 65 years and requiring intravenous medication sedation for acute agitation were enrolled and randomized to an intravenous bolus of midazolam 5 mg–droperidol 5 mg, droperidol 10 mg, or olanzapine 10 mg. Two additional doses were administered, if required: midazolam 5 mg, droperidol 5 mg, or olanzapine 5 mg. The primary outcome was the proportion of patients adequately sedated at 10 minutes.

Results: Three hundred forty-nine patients were randomized to the 3 groups. Baseline characteristics were similar across the groups. Ten minutes after the first dose, significantly more patients in the midazolam-droperidol group were adequately sedated compared with the droperidol and olanzapine groups: differences in proportions 25.0% (95% confidence interval [CI] 12.0% to 38.1%) and 25.4% (95% CI 12.7% to 38.3%), respectively. For times to sedation, the differences in medians between the midazolam-droperidol group and the droperidol and olanzapine groups were 6 (95% CI 3 to 8) and 6 (95% CI 3 to 7) minutes, respectively. Patients in the midazolam-droperidol group required fewer additional doses or alternative drugs to achieve adequate sedation. The 3 groups' adverse event rates and lengths of stay did not differ.

Conclusion: Midazolam-droperidol combination therapy is superior, in the doses studied, to either droperidol or olanzapine monotherapy for intravenous sedation of the acutely agitated ED patient. [Ann Emerg Med. 2016;■:1-9.]

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INTRODUCTION

Background

Acute agitation among emergency department (ED) patients is often associated with recreational drug or alcohol intoxication, mental illness, or combinations of diagnoses.[1-5] The agitation may escalate to violence that is disruptive and associated with a risk of injury to the patient and individuals around them.[3,6] These events usually result in a "security code" being called for an unarmed threat. De-escalation techniques are recommended initially,[7] although parenteral medication sedation may be required.[3,5,6]

Importance

Sedation for acute agitation is required in 3 to 20 cases for every 1,000 ED presentations[3,6] and the risk to the patient is real. Adverse effects are common and include airway compromise, oxygen desaturation, hypotension, and extrapyramidal events.[3,5,8-12] The challenge is to use a medication regimen that will rapidly and effectively sedate the patient without putting him or her at substantial risk of adverse events. To date, a wide range of regimens has been used, mostly including benzodiazepines or antipsychotic medications administered by either the intramuscular or intravenous route.[4,8,9,13-15]

Most studies of acute agitation have been undertaken in the psychiatric setting. Hence, most evidence is not directly applicable to the ED, where the onset of sedation needs to be rapid and where the pathogenesis of the agitation is often undifferentiated.[5] Currently, ED sedation guidelines are often inconsistent, poorly supported by evidence, and frequently not followed.[13] Furthermore, sedation practice is evolving, with new medications being incorporated into practice in unapproved settings or routes of administration, eg, intravenous olanzapine.[16]

Editor's Capsule Summary

What is already known on this topic

Emergency physicians often treat acutely agitated patients with antipsychotics, benzodiazepines, or both.

What question this study addressed

Is adequate sedation after 10 minutes more frequent with droperidol 10 mg, olanzapine 10 mg, or midazolam 5 mg plus droperidol 5 mg?

What this study adds to our knowledge

In this randomized controlled trial of 349 adults with acute agitation, at 10 minutes after administration, 25% more patients in the midazolam-droperidol group had achieved adequate sedation than had the group with the other agents, with a similar frequency of adverse events.

How this is relevant to clinical practice

Combination midazolam 5 mg plus droperidol 5 mg is more effective for acute agitation than either droperidol 10 mg or olanzapine 10 mg.

Goals of This Investigation

Recent research suggests that medication combination regimens are superior to monotherapy.[1,13,15] Chan et al[1] reported that both intravenous midazolam-droperidol and intravenous midazolam-olanzapine combinations are superior to intravenous midazolam monotherapy. The relevance of this finding is that benzodiazepine monotherapy, especially midazolam, is currently the most commonly used regimen for acute agitation management in some parts of the world.[13,15] Droperidol[4,13,15] and, more recently, olanzapine[4,12,16,17] are also used as monotherapy. To date, the efficacy of the midazolam-droperidol combination in acute agitation has not been compared with either droperidol or olanzapine monotherapy. We compared these 3 regimens and hypothesized that the midazolam-droperidol combination would be the superior regimen.

MATERIALS AND METHODS

Study Design and Setting

We undertook a randomized, controlled, double-blind, triple-dummy, clinical trial in the EDs of 2 inner-city, tertiary-referral, Australian hospitals with an annual census of 45,000 adult patients for one and 70,000 for the other. Each ED is supported by 24 hour colocated psychiatric services. Patients were enrolled between October 2014 and August 2015. The trial was registered on the Australian and New Zealand Clinical Trials Registry and approved by the human research ethics committees of the participating institutions.

Selection of Participants

Patients were eligible for inclusion if they were aged 18 to 65 years and required intravenous medication sedation for acute agitation, as determined by their attending emergency physician. Patients were excluded if they had been previously enrolled, had a known hypersensitivity or contraindication to a study medication, had a reversible cause for their agitation (hypotension, hypoxia, or hypoglycemia), were experiencing acute alcohol withdrawal, or were pregnant.

Enrollment was based on patient and staff safety considerations and not sedation scores. Patients who received a sedative medication within the previous 12 hours, either as usual medications or out-of-hospital treatment, were eligible if they met other eligibility criteria. Because of the level of agitation, informed patient consent was not possible and human research ethics committee approval was given for waiver of consent.

Methods of Measurement

Patients were assigned to a midazolam-droperidol combination arm, a droperidol monotherapy (droperidol) arm, or an olanzapine monotherapy (olanzapine) arm (Figure 1). The first and additional doses, respectively, were midazolam 5 mg plus droperidol 5 mg and midazolam 5 mg, droperidol 10 and 5 mg, and olanzapine 10 and 5 mg (Appendix E1, available online at http://www.annemergmed.com). Doses were determined from clinical practice[13,16,17] and previous trials[1,5] and were administered by rapid intravenous push. The midazolam-droperidol combination was chosen over midazolam-olanzapine because droperidol is more commonly used.[13,18]

Study packs were assembled by the pharmacy department of a third hospital. Each contained a patient identification code, instructions, a case report form, vials of repackaged medication or placebo, water for reconstitution, normal saline solution for dilution, disposables (eg, needles, syringes), and a sealed envelope with a description of the vial contents (if unblinding were required).

At each site, study packs were block randomized in groups of 6 (2 for each study arm) to ensure approximately equal numbers of patients in each arm. A pharmacist not involved with patient enrollment, data collection, or data analysis conducted the randomization with random-number tables and kept the codes confidential.

Midazolam and droperidol are clear liquids. Olanzapine is a yellow powder that requires reconstitution to a yellow liquid. To achieve blinding, a triple-dummy technique was

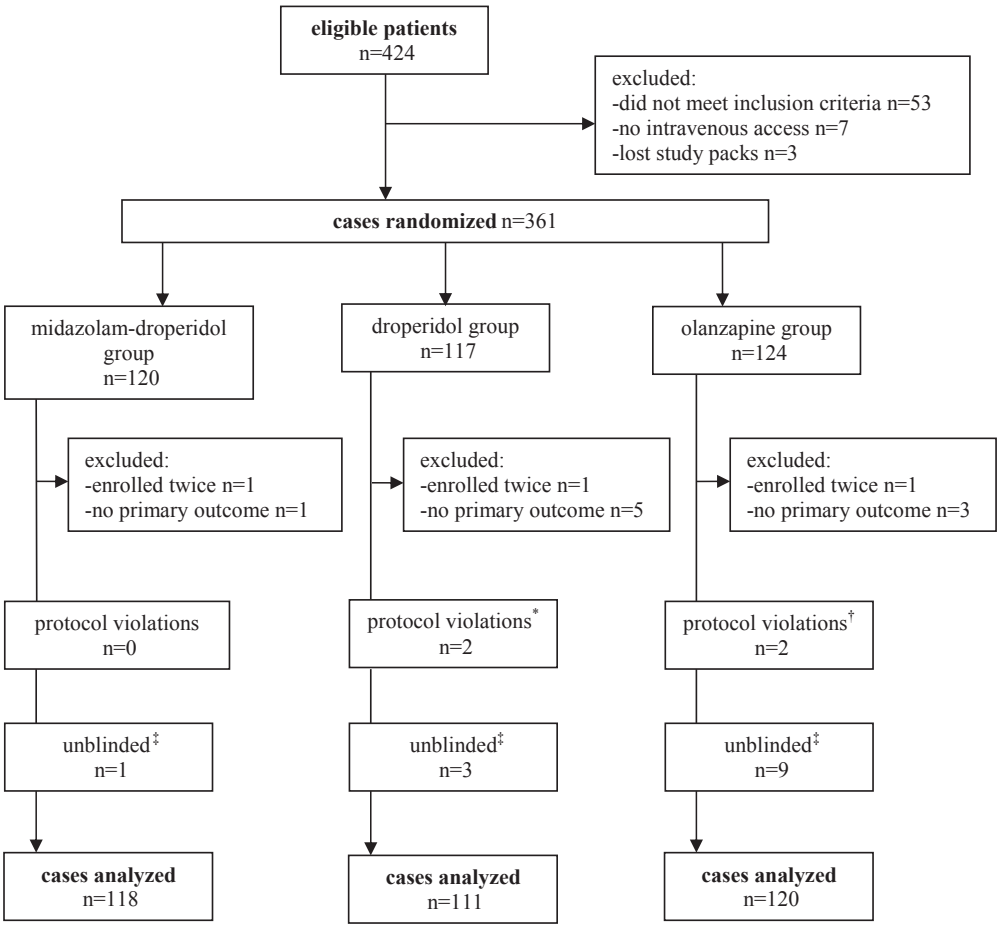

Figure 1. Patient flow through the study (modified CONSORT diagram). *Patients aged 15 and 71 years. †Patients aged 68 and 69 years. ‡Patient sedation difficult and unblinding undertaken to inform clinical decisionmaking. No unblinding was undertaken in response to adverse events.

used. Normal saline solution was used for the clear liquid placebos. Soluvit N (Fresenius Kabi Australia Pty Limited, Pymble, NSW, Australia), a vitamin and mineral preparation designed for intravenous parenteral nutrition, was used as the olanzapine placebo and has been used successfully as such.[1]

Consecutive patient enrollment was undertaken by assigning patients to the next sequential study pack at their site. Details of the vial contents and preparation, the administered volumes, and doses are described in Appendix E1 (available online at http://www.annemergmed.com).

If adequate sedation was not achieved within 5 minutes of the first dose, an additional dose was administered. A second additional dose was administered 5 minutes later, if required. If adequate sedation was not achieved 5 minutes after the second additional dose, the emergency physician could administer additional, open-label, sedative medication(s) at his or her discretion. At this stage, the physician could unblind the study medication if this was deemed necessary for patient safety.

Senior ED nurses recorded the level of patient sedation and all adverse events and their management. Patient sedation was measured with a 6-point, validated sedation scale[19] (5=highly aroused, violent; 4=highly aroused, possibly distressed, or fearful; 3=moderately aroused, unreasonable, or hostile; 2=mildly aroused, willing to talk reasonably; 1=minimal agitation; and 0=asleep). Scores were recorded at baseline (immediately before first dose administration) and every 5 minutes until 60 minutes after sedation was achieved. Adequate sedation was defined as a score less than or equal to 2 or when no further sedation was required, as determined by the treating physician. All patients received standard sedation care, including 1:1 nursing and regular monitoring of sedation level, vital signs, cardiac rhythm, and adverse events.

Outcome Measures

The primary outcome was the proportion of patients adequately sedated within 10 minutes of the first dose administration.

The secondary outcomes included time to adequate sedation, the need for resedation less than 60 minutes after achieving sedation, resedation from 60 minutes after sedation until ED discharge, sedation medication failure (alternate medications required), ECG QTc interval, and adverse events.

Primary Data Analysis

Chan et al[1] reported that the proportion of patients adequately sedated at 10 minutes in their midazolam-droperidol arm was 66.1%. We determined that a proportion less than two thirds of this proportion (ie, 44%) would represent a clinically significant difference between the midazolam-droperidol and either of the other arms. To demonstrate this difference in the proportions (66% versus 44%), at least 114 patients were required in each arm (2-sided; power 0.9; $P<.05$). Hence, a sample size of at least 342 patients was required.

Data analysis used the intention-to-treat principle. Most data are presented descriptively, including graphically. The proportions of patients adequately sedated at 10 minutes were analyzed with differences in proportions (95% confidence intervals [CIs]). Time to sedation was analyzed with difference in medians (95% CI) and survival-time data and was plotted with a Kaplan-Meier curve. Hazard ratios (95% CI) for adequate sedation were generated with the midazolam-droperidol group as a baseline reference, and multivariable Cox regression was used to adjust for regular medications and medications administered before the study medication. IBM SPSS (version 23; IBM Corp., Armonk, NY) was used for all analyses. Unblinding was undertaken only after all analyses were complete.

RESULTS

Characteristics of Study Subjects

Of 424 patients screened, 361 were enrolled (Figure 1). An additional 12 patients were excluded for either missing primary endpoint data or repeated enrollment. Data from the remaining 349 patients (96.7% of those eligible) were analyzed. The patient baseline characteristics are reported in Table 1. For these characteristics, the gross magnitude of the differences between the groups does not appear large enough to confound the analysis.

Main Results

Ten minutes after the first sedative dose, significantly more patients in the midazolam-droperidol group were adequately sedated compared with those in the droperidol and olanzapine groups (differences in proportions 25.0% [95% CI 12.0% to 38.1%] and 25.4% [95% CI 12.7% to 38.3%], respectively). At each point after the first dose, significantly fewer patients were adequately sedated in the droperidol and olanzapine groups (hazard ratios 0.53 [95% CI 0.41 to 0.69] and 0.50 [95% CI 0.39 to 0.65], respectively) (Table 2, Figure 2). The multivariable Cox regression indicated that other medications had negligible effect on the hazard ratios.

The median time to adequate sedation for the midazolam-droperidol group was significantly shorter than for both the droperidol and olanzapine groups (Table 2). The differences in medians for times to sedation between the midazolam-droperidol and droperidol, and midazolam-droperidol and olanzapine groups were 6 minutes (95% CI 3 to 8 minutes) and 6 minutes (95% CI 3 to 7 minutes), respectively.

Fewer patients in the midazolam-droperidol group required additional doses or medications other than additional doses (Table 3). The groups did not differ in the proportion of patients who required resedation after initial adequate sedation had been achieved.

The proportion of patients in each group who experienced an adverse event did not differ (Table 4). Most events were related to respiratory depression and were readily managed, with no patient requiring intubation.

An ECG was obtained within 30 minutes of the first dose for 193 patients (55.3%): midazolam-droperidol 71 (60.2%), droperidol 61 (55.0%), and olanzapine 61 (50.8%). The median QTc intervals of the 3 groups were similar: 450 ms (range 325 to 501 ms), 442 ms (range 320 to 501 ms), and 445 ms (range 313 to 501 ms), respectively. No patient experienced a cardiac adverse event.

There were a total of 4 protocol violations (Figure 1). All occurred because the patients' ages were not known when sedation was deemed necessary. The study age criteria were established for safety reasons only. The 4 patients were included in the data analysis because of our intention-to-treat analysis. Reanalysis of the data after their exclusion did not change the results.

The median ED lengths of stay for the midazolam-droperidol, droperidol, and olanzapine groups were similar: 11.0 hours (interquartile range 7.0 to 14.6 hours), 9.1 hours (interquartile range 6.2 to 13.3 hours), and 10.7 hours (interquartile range 7.3 to 14.8 hours), respectively. The groups did not differ in places of patient disposition after ED discharge. In each group, slightly more than half of patients were discharged home and approximately one quarter were admitted to a psychiatric ward. The remaining patients were discharged to observation or medical wards, police or correctional facilities, or assisted accommodation. Six patients absconded.

Table 1. Baseline patient characteristics.

Patient Variable	Midazolam-Droperidol, n=118	Droperidol, n=111	Olanzapine, n=120
Age, mean (95% CI), y	34 (32–36)	34 (32–36)	35 (33–37)
Male, No. (%)	72 (61.0)	68 (61.3)	69 (57.5)
ATS category, No. (%)			
1, Resuscitation	5 (4.2)	6 (5.4)	9 (7.5)
2, Emergency	40 (33.9)	50 (45.0)	50 (41.7)
3, Urgent	69 (58.5)	49 (44.1)	56 (46.7)
4, Semiurgent	4 (3.4)	6 (5.4)	5 (4.2)
5, Nonurgent	0	0	0
Waiting time from triage to be seen by a physician, median (IQR), min	23 (4–53)	12 (4–31)	21 (3–44)
***ICD-10* category, No. (%)**			
Intoxication (drugs or alcohol)	57 (48.3)	61 (55.0)	65 (54.2)
Mental illness[†]	56 (47.5)	45 (40.5)	47 (39.2)
Organic illness[‡]	5 (4.2)	5 (4.5)	8 (6.6)
Substance abuse history,[§] No. (%)	95 (80.5)	103 (92.8)	100 (83.3)
Usual psychotropic medications, No. (%)	33 (28.0)	29 (26.1)	34 (28.3)
Benzodiazepines	8 (6.8)	4 (3.6)	6 (5.0)
SSRI or SNRI	6 (5.1)	7 (6.3)	7 (5.8)
Atypical antipsychotics	10 (8.5)	14 (12.6)	18 (15.0)
Depot antipsychotics	2 (1.7)	4 (3.6)	3 (2.5)
Conventional antipsychotics	5 (4.2)	3 (2.7)	3 (2.5)
Need for physical restraint, No. (%)	85 (72.0)	86 (77.5)	93 (77.5)
Sedatives before enrollment,[¶] No. (%)	32 (27.1)	30 (27.0)	26 (21.7)
Police attendance on arrival, No. (%)	80 (67.8)	78 (70.3)	93 (77.5)
Mode of arrival, No. (%)			
Road ambulance	69 (58.5)	67 (60.4)	69 (57.5)
Police	41 (34.8)	37 (33.3)	42 (35.0)
Other[‖]	8 (6.7)	7 (6.3)	9 (7.5)

ATS, Australasian Triage Scale; *IQR*, interquartile range; *ICD-10*, *International Classification of Diseases, 10th Revision*; *SSRI*, selective serotonin-reuptake inhibitor; *SNRI*, serotonin noradrenaline-reuptake inhibitor.

[†]Mental illness includes psychoses, anxiety, depressive illnesses, and trauma as a consequence of suicide attempt.

[‡]Organic illness includes infections, delirium because of an organic cause, and all other trauma.

[§]Substances include drugs or alcohol.

[¶]Sedatives (ie, benzodiazepines and antipsychotics) before study enrollment included those administered in the out-of-hospital care setting (ie, administered by paramedics) or in the ED.

[‖]Other modes of transport include private travel (ie, self, family, or friends).

LIMITATIONS

A slightly greater proportion of the midazolam-droperidol group had less urgent triage categories, a history of mental illness, and a disposition to a psychiatry ward. However, these differences were minor and unlikely to have introduced confounding. Additionally, our analysis did not account for multiple comparisons.

The sedation scale was potentially subject to measurement bias. However, it has been validated, the ED staff were fully trained in its use, and it has proven reliable in our earlier trials.[1,5] Also, any bias was likely to have been evenly distributed across all groups and minimized by blinding of the ED staff.

Almost half of all patients did not have an ECG recorded, and this may have introduced selection bias. Although unlikely, it is possible that some patients with substantial QTc abnormalities were not identified.

In this study, the first and additional doses for each group were equivalent (total 10 and 5 mg, respectively). However, it was not simply assumed that the potencies at these doses would be equivalent. All doses were determined by careful examination of the doses commonly used in clinical practice[13] and our earlier trials.[1,5]

Table 2. Proportions of patients sedated at specific points after first dose administration and median times to adequate sedation.

Outcome Variable	Midazolam-Droperidol, n=118	Droperidol, n=111	Olanzapine, n=120
Proportion sedated, No. (%)			
at 5 min	66 (55.9)	27 (24.3)	35 (29.2)
at 10 min	88 (74.6)	55 (49.6)	59 (49.2)
at 15 min	105 (89.0)	67 (60.4)	79 (65.8)
at 30 min	113 (95.8)	92 (82.9)	96 (80.0)
at 60 min	116 (98.3)	106 (95.5)	109 (90.8)
Time to sedation, median (IQR), min	5 (3–11)	11 (6–23)	11 (5–25)

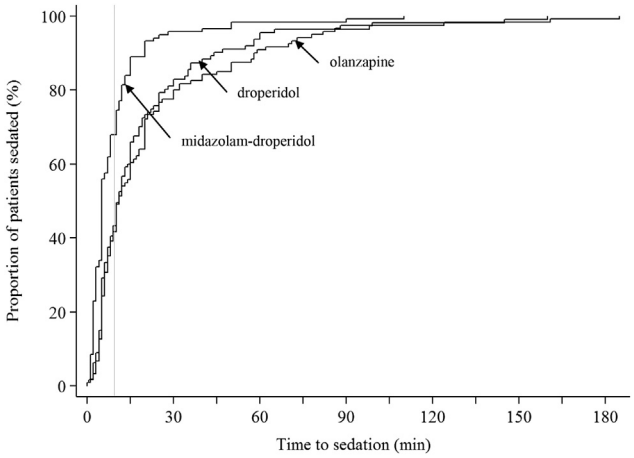

Figure 2. Kaplan-Meier curve comparing the proportion of patients sedated as a function of time. The vertical line is at 10 minutes, with the proportion sedated at the time of the primary outcome of the study.

The internal validity of this study should be maximized by the use of very similar peer-reviewed methodology.[1,5] Because patients were enrolled at only 2 centers, the external validity may be questionable. However, our patients are likely to be similar to those from other centers.

DISCUSSION

This study demonstrates that, in the doses studied, a midazolam-droperidol combination is significantly more efficacious than droperidol or olanzapine monotherapy in achieving rapid and adequate sedation. This is evidenced by higher proportions of patients sedated at any point, shorter times to sedation, and lower proportions requiring additional sedatives with the combination regimen.

The adverse event profiles of the 3 regimens did not differ, although respiratory events were slightly more common in the midazolam-droperidol group. This is consistent with reports of respiratory compromise associated with midazolam sedation for both acute agitation[1,5] and painful procedures.[20] The incidence of acute dystonia was low.

Because the midazolam-droperidol combination in this study was identical to that of Chan et al,[1] the two can be compared directly. The median times to sedation for the 2 midazolam-droperidol groups were 5 and 6 minutes, respectively. This similarity provides strong and consistent evidence of the efficacy of this midazolam-droperidol combination. Although the proportions of patients adequately sedated at 5 minutes differed (55.9% versus 35.7%, respectively), this was likely due to differences in patient characteristics. In particular, there were more intoxicated (drugs or alcohol) patients in the current study (48.3% versus 30.4%, respectively).

The midazolam-droperidol combination has been examined previously. Chan et al[1] reported that it has similar effectiveness and safety profiles as the midazolam-olanzapine combination. Although the midazolam-olanzapine

Table 3. Secondary endpoints, the need for additional parenteral sedative medication (patients may be administered more than one medication).

Additional Mediations Administered	Midazolam-Droperidol, n=118	Droperidol, n=111	Olanzapine, n=120
Number of additional doses required to reach initial adequate sedation, No. (%)			
0	85 (72.0)	45 (40.5)	47 (39.2)
1	25 (21.2)	30 (27.0)	29 (24.2)
2	8 (6.8)	36 (32.4)	44 (36.7)
Need for additional parenteral medications to reach initial adequate sedation, No. (%)*	2 (1.7)	15 (13.5)	31 (25.8)
Midazolam	2 (1.7)	12 (10.8)	27 (22.5)
Droperidol	0	5 (4.5)	9 (7.5)
Olanzapine	2 (1.7)	1 (0.9)	8 (6.7)
Ketamine	0	1 (0.9)	0
Need for additional parenteral resedation <60 min after initial adequate sedation, No. (%)	7 (5.9)	5 (4.5)	10 (8.3)
Midazolam	5 (4.2)	3 (2.7)	8 (6.7)
Droperidol	3 (2.5)	2 (1.8)	3 (2.5)
Olanzapine	3 (2.5)	1 (0.9)	4 (3.3)
Ketamine	0	1 (0.9)	0
Need for additional parenteral resedation from 60 min after initial adequate sedation until ED discharge, No. (%)	26 (22.0)	16 (14.4)	28 (23.3)
Midazolam	18 (15.3)	12 (10.8)	23 (19.2)
Droperidol	14 (11.9)	4 (3.6)	9 (7.5)
Olanzapine	8 (6.8)	4 (3.6)	9 (7.5)
Ketamine	0	1 (0.9)	1 (0.8)

*Additional parenteral sedatives include medication doses required in addition to the study medication additional doses.

Table 4. Reported adverse events.

Adverse Events	Midazolam-Droperidol, n=118	Droperidol, n=111	Olanzapine, n=120
Number of patients with reported events, No. (%)*	26 (22.0)	18 (16.2)	24 (20.0)
Airway obstruction†	11 (9.3)	4 (3.6)	5 (4.2)
Oxygen desaturation† (SaO_2 <90%)	17 (14.4)	7 (6.3)	13 (10.8)
Hypotension‡ (SBP <80 mm Hg)	2 (1.7)	4 (3.6)	1 (0.8)
Bradycardia (PR <60 beats/min)	0	2 (1.8)	5 (4.2)
Prolonged QTc§ (QTc interval >500 ms)	1 (0.8)	3 (2.7)	3 (2.5)
Acute dystonia‖	1 (0.8)	0	2 (1.7)
Hypoventilation (RR <10 breaths/min)	0	1 (0.9)	1 (0.8)

SBP, Systolic blood pressure; *PR*, pulse rate; *RR*, respiratory rate.
*Patients may have experienced more than 1 event.
†All cases of airway obstruction and oxygen desaturation were transient and resolved with jaw thrust or lateral positioning, with or without supplemental oxygen.
‡All cases resolved after the administration of fluids, without sequelae.
§No clinical symptoms, and no treatment was required for all cases of prolonged QTc.
‖All cases resolved without sequelae; 1 case in the olanzapine group required benztropine.

combination has not been directly compared with droperidol or olanzapine monotherapy, it is likely that this combination may serve as an effective alternative in jurisdictions where droperidol is not used.

Traditionally, monotherapy, administered either intravenously or intramuscularly, has been used for the sedation of acutely agitated ED patients.[4,9,13] Trials have examined benzodiazepines (midazolam, diazepam, lorazepam, and clonazepam),[1,5,8,11,21-23] conventional antipsychotics (chlorpromazine, haloperidol, and droperidol),[5,8,10,11,13,21-26] and atypical antipsychotics (olanzapine and ziprasidone).[13,21,27-29] There is now increasing interest in medication combinations. The effectiveness of several combinations has been examined, including benzodiazepine-droperidol,[1] benzodiazepine-olanzapine,[1,30] benzodiazepine-haloperidol,[8,30] and haloperidol-promethazine.[11,24,28,31]

Although monotherapy may be simpler to administer, its mechanisms are largely limited to single biochemical pathways. Unfortunately, trials of medication combinations have suffered from uncontrolled medication redosing, lack of blinding, and settings other than the ED.[8,11,24,28,31] There is, however, some evidence that combinations produce more rapid sedation,[1,13,15] less need for resedation,[1] and reduced benzodiazepine dosage[1] and have comparable adverse event profiles.[1] Because most studies of combination therapy have used the intramuscular route, comparisons with this study are difficult. To our knowledge, this is only the second study to have examined intravenous medication combinations.[1]

Sedation with droperidol is becoming increasingly common.[4,6,13] However, its widespread use is hindered by a black box warning related to QTc interval prolongation.[32] There is now increasing evidence that droperidol has a good safety profile in the ED setting.[1,3,5,14,23,25] In a position statement, Perkins et al[33] described droperidol as effective and safe. The findings of our trial provide additional evidence for the safety of droperidol.

Olanzapine has a relatively benign adverse effect profile. However, a Cochrane review[27] of intramuscular olanzapine for acutely agitated patients concluded that published studies had poorly reported outcomes and the potential for bias. No trials in the ED setting were included. Subsequently, one ED study supported the safety of olanzapine administered by the intramuscular route.[30] Olanzapine is increasing being used intravenously (off label),[13,16,17] and one retrospective study supports the safety of intravenous olanzapine in the ED setting.[29] To date, only one clinical trial has examined its effects through the intravenous route.[1] In that study, it appeared safe at the 5-mg dose and in combination with midazolam.[1] The present study provides additional evidence that intravenous olanzapine is safe.

Both intravenous and intramuscular routes are commonly used for sedative medication administration. The intravenous and intramuscular routes are preferred in Australasia[13] and Hong Kong,[15] respectively. The intravenous route is often recommended[7,19,34,35] because the intramuscular route may be unpredictable, may have a slower onset, and cannot be used for accurate titration. However, intravenous administration requires cannulation of the patient. This usually requires physical restraint, which may not be an option in EDs with limited security or ED staff resources. To date, to our knowledge no published clinical trials have compared the effectiveness of sedatives administered by these two routes.

In summary, this study demonstrates that, in the doses studied, the intravenous midazolam-droperidol

combination provides significantly more rapid and effective sedation than the intravenous droperidol or olanzapine monotherapy regimens. Also, it required fewer additional doses or other medications to achieve adequate sedation. It is recommended that the midazolam-droperidol combination be used for the sedation of acutely agitated ED patients regardless of whether the cause of the agitation is known.

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APPENDIX E1

Medication Vial Preparation and Dosage Regimen

Medication vial preparation:

After enrollment, the 2 clear liquid vials (A and B) were drawn up and the yellow powder vial (C) was reconstituted and drawn up. The first dose of sedative(s) comprised contents from all 3 vials (2 clear and 1 yellow liquid). Additional doses, if required, comprised contents from 2 vials only (1 clear and 1 yellow liquid).

Medication regimen:

1. Midazolam-droperidol combination (control) arm*:

	Vial A, Midazolam, 15 mg/15 mL, Clear Solution	Vial B, Droperidol, 5 mg/2 mL, Clear Solution	Vial C, Placebo, 2×, 10 mL, Yellow Solution
First dose, mg (mL)	5 (5)	5 (2)	0 (10)
First additional dose, if required, mg (mL)	5 (5)	No dose	0 (5)
Second additional dose, if required, mg (mL)	5 (5)	No dose	0 (5)

*Minimum (maximum) total dose: midazolam 5 mg (15 mg), droperidol 5 mg (5 mg).

2. Droperidol monotherapy (droperidol) arm*:

	Vial A, Droperidol, 15 mg/15 mL, Clear Solution	Vial B, Droperidol, 5 mg/2 mL, Clear Solution	Vial C, Placebo, 2×, 10 mL, Yellow Solution
First dose, mg (mL)	5 (5)	5 (2)	0 (10)
First additional dose, if required, mg (mL)	5 (5)	No dose	0 (5)
Second additional dose, if required, mg (mL)	5 (5)	No dose	0 (5)

*Minimum (maximum) total dose: droperidol 10 mg (20 mg).

3. Olanzapine monotherapy (olanzapine) arm*:

	Vial A, Placebo, 15 mL, Clear Solution	Vial B, Placebo, 2 mL, Clear Solution	Vial C, Olanzapine, 2×, 10 mg/10 mL, Yellow Solution
First dose, mg (mL)	0 (5)	0 (2)	10 (10)
First additional dose, if required, mg (mL)	0 (5)	No dose	5 (5)
Second additional dose if required, mg (mL)	0 (5)	No dose	5 (5)

*Minimum (maximum) dose: olanzapine 10 mg (20 mg).