Intravenous Droperidol or Olanzapine as an Adjunct to Midazolam for the Acutely Agitated Patient: A Multicenter, Randomized, Double-Blind, Placebo-Controlled Clinical Trial

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Study objective: Parenteral benzodiazepines or antipsychotics are often used to manage acute agitation in emergency department (ED) settings in which alternative strategies have failed or are not feasible. There are scant data comparing parenteral medication regimens. We aim to determine the efficacy and safety of intravenous droperidol or olanzapine as an adjunct to intravenous midazolam for rapid patient sedation.

Methods: We undertook a randomized, double-blind, placebo-controlled, double-dummy, clinical trial in 3 EDs (August 2009 to March 2011). Adult patients (n=336) requiring intravenous drug sedation for acute agitation were randomized to receive a saline solution (control), droperidol (5 mg), or olanzapine (5 mg) bolus. This was immediately followed by incremental intravenous midazolam boluses (2.5 to 5 mg) until sedation was achieved. The primary outcome was time to sedation. Secondary outcomes were need for "rescue" drugs and adverse events.

Results: Three hundred thirty-six patients were randomized to the 3 groups. Baseline characteristics were similar across groups. The differences in medians for times to sedation between the control and droperidol and control and olanzapine groups were 4 minutes (95% confidence interval [CI] 1 to 6 minutes) and 5 minutes (95% CI 1 to 6 minutes), respectively. At any point, patients in the droperidol and olanzapine groups were approximately 1.6 times more likely to be sedated compared with controls: droperidol and olanzapine group hazard ratios were 1.61 (95% CI 1.23 to 2.11) and 1.66 (95% CI 1.27 to 2.17), respectively. Patients in the droperidol and olanzapine groups required less rescue or alternative drug use after initial sedation. The 3 groups' adverse event profiles and lengths of stay did not differ.

Conclusion: Intravenous droperidol or olanzapine as an adjunct to midazolam is effective and decreases the time to adequate sedation compared with midazolam alone. [Ann Emerg Med. 2013;61:72-81.]

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INTRODUCTION

Background

Agitation and aggression are commonly manifested by patients in the emergency department (ED) as a consequence of mental illness, drug and alcohol intoxication, or both.[1-5] Parenteral drug sedation may be required to manage these patients if de-escalation strategies or oral drug sedation either fails or is not feasible. Studies in EDs have compared 2 main pharmacologic classes, namely, benzodiazepines (eg, midazolam,[6-9] lorazepam[6,10,11]) and antipsychotics (eg, droperidol,[7-10,12] haloperidol,[6,11,12] ziprasidone[7]). Because most studies[6-8,10,12] have compared one drug class to another and a single drug in each arm, they provide insufficient evidence on the use of concurrent sedating agents (ie, combination therapy).

Combination therapy for rapid sedation (especially by the intravenous route) is common practice in the ED setting. A recent survey of Australasian ED practitioners[13] found that, although intravenous midazolam was the preferred drug, intravenous droperidol or intravenous olanzapine was used as an adjunct to midazolam by 18.4% or 16.0% of respondents, respectively, for sedation of undifferentiated acutely agitated patients. Although haloperidol is used in combination with midazolam, its general use is declining considerably.[13,14] Theoretically, intravenous midazolam-droperidol and midazolam-olanzapine combinations should produce rapid

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

Does combining an antipsychotic with midazolam shorten time to sedation?

What this study adds to our knowledge

In this randomized controlled trial of 336 adults with acute agitation, adding either droperidol or olanzapine to midazolam shortened time to sedation by a median of 4 or 5 minutes, respectively, with similar adverse events.

How this is relevant to clinical practice

Combination antipsychotic/midazolam therapy for acute agitation provides faster sedation than midazolam alone.

sedation and reduce overall drug dosage and the need for resedation.

Importance

Although combination therapy is believed to produce a rapid onset of sedation, lessen the requirement for resedation, and reduce benzodiazepine doses,[15] there are insufficient data to support such combinations.[16] To date, most trials exploring the use of combination therapy have been undertaken in non-ED settings and have suffered methodological deficiencies.[11,13,17,18] Additionally, debate persists[19-23] around the "black box" warning for droperidol that is related to prolonged QT and torsades de pointes.[24] This has led to recommendations for additional clinical trials,[25] especially because droperidol remains in use in the ED setting.[7,13,26] Finally, although intramuscular olanzapine has a relatively benign adverse effect profile in the acute setting, it is increasingly being used (off label) intravenously.[27,28]

Goals of This Investigation

This study compared the efficacy and safety of intravenous droperidol (5 mg) or olanzapine (5 mg) boluses as an adjunct to midazolam with midazolam monotherapy as a sedating agent for the management of acute agitation in the ED setting.

MATERIALS AND METHODS

Study Design and Setting

A multicenter, randomized, double-blind, placebo-controlled, double-dummy, clinical trial was undertaken in 3 large metropolitan EDs between August 2009 and March 2011. These EDs are tertiary referral centers, with annual censuses of 40,000 to 70,000 patients and 24-hour colocated psychiatric services. The trial was registered on the Australian and New Zealand Clinical Trials Registry (ACTRN 12607000591459).

Selection of Participants

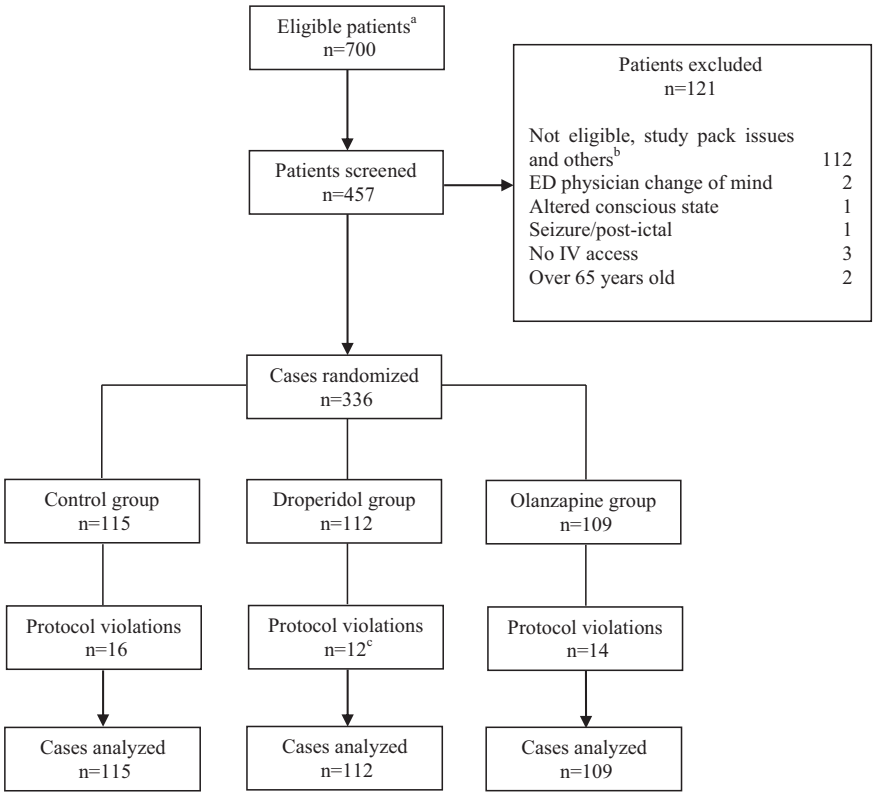
Inclusion criteria were aged 18 to 65 years and the need for parenteral drug sedation for acute agitation, as determined by a registrar (senior resident) or consultant emergency physician. Enrollment was not based on sedation score but determined by the physician. All patients were highly agitated, defined as requiring immediate intravenous sedative containment. Exclusion criteria were known hypersensitivity or contraindication to midazolam, droperidol, or olanzapine; obvious reversible cause for agitation (eg, hypotension, hypoxia, hypoglycemia); known pregnancy; and acute alcohol withdrawal. Patients who had recently received (within the previous 12 hours) oral or parenteral sedative drug(s), either as usual medications or out-of-hospital acute agitation treatment, were eligible if they met other eligibility criteria. Enrollment was initiated by the treating physician.

The study was authorized by the human research ethics committees of the participating hospitals and an affiliated university. Waiver of informed consent was granted and is discussed elsewhere.[29] A data safety and monitoring committee oversaw study procedures and adverse events.

Methods of Measurement

Computerized block randomization (blocks of 6), stratified by study site, was performed by an independent pharmacist. After enrollment, patients were assigned to the next study pack in the allocated sequence. All patients, ED staff, and study personnel remained blinded to group allocation until data entry and analyses were completed.

Patients were randomized to one of 3 groups and received adjunct boluses of intravenous sedating drugs or placebos (Figure 1): control group (placebo-droperidol, placebo-olanzapine), droperidol group (droperidol 5 mg, placebo-olanzapine), and olanzapine group (olanzapine 5 mg, placebo-droperidol). The choice of midazolam alone as the control group was supported by the results of an Australasian survey of emergency physicians, which showed that midazolam was the most commonly used sedating drug, either alone or in combination.[13] Drug doses were based on the same survey, although, given the lack of evidence about the safety of intravenous olanzapine (especially in combination), the olanzapine starting dose was deliberatively conservative. The "double dummy" technique was used with normal saline solution as placebo-droperidol and Soluvit N (Fresenius Kabi Australia Pty Ltd, Pymble, New South Wales, Australia), a yellow powdered intravenous nutritional supplement, as placebo-olanzapine. The appearance of the drug vials and the dosage instructions for the placebo and active study drugs were identical. The study bolus drugs (saline solution, droperidol,



ED, Emergency Department; IV, Intravenous. [a]Estimation of total eligible patients prior to patient randomization across all study sites, based on the proportion of patients requiring parenteral drug sedation in Victorian EDs[27]; [b]Patient did not meet entrance criteria, change in patient status, pack discarded or lost, unspecified reason; [c]Thirteen protocol violations among 12 patients, one patient with two protocol violations.

Figure 1. Patient flow through the study (modified Consolidated Standards of Reporting Trials [CONSORT] diagram).

olanzapine) were repackaged by an independent pharmacist before insertion into the study packs. Accompanying instructions were to administer the total contents of the clear liquid vial (saline solution or droperidol) and half the contents of the reconstituted yellow powder vial (placebo or olanzapine).

Immediately after the adjunct boluses, each patient received intravenous midazolam (2.5 mg or 5 mg for estimated weights of $<$50 kg and $\geq$50 kg, respectively) followed by incremental doses of midazolam until adequate sedation was achieved. Sedation was measured with a 6-point, validated sedation scale (5=highly aroused, violent toward self, others, or property; 4=highly aroused and possibly distressed or fearful; 3=moderately aroused, agitated, more vocal, unreasonable, or hostile; 2=mildly aroused, pacing, willing to talk reasonably; 1=settled, minimal agitation; and 0=asleep).[30,31] Adequate sedation was defined as a score less than or equal to 2. The scale was developed to monitor changes in agitation levels and is similar to another scale used in previous agitation research.[8] Before study commencement, all staff were trained in the use of the scale during in-service sessions and encouraged to incorporate it into their usual practice.

The treating physician determined the need for subsequent intravenous midazolam doses (up to a cumulative dose of 20 mg). The dose and timing of additional midazolam were not specified because they depended on the clinical response. The treating physician would prescribe additional doses until adequate sedation (sedation scale score $\leq$2) had been achieved. The objective was to conduct a pragmatic trial, in which the physicians would be redosing according to their usual clinical judgment and patient response. A particular scale score (eg, 4) would not automatically trigger an additional dose. The only requirement was for patients to be sedated to the clinical endpoint defined as a sedation score less than or equal to 2. Beyond the 20-mg cumulative midazolam dose, the physicians could unblind the group allocation by opening a sealed, opaque envelope in the study pack if they thought this was necessary to guide further management. The sealed envelope was otherwise returned as proof of blinding. The use of any other drugs, interventions, or procedures thought to be necessary was permitted, and they were administered until adequate sedation was reached. All patients received standard institutional care for rapid sedation, including 1:1 nursing and monitoring for the adequacy of sedation, hypoxia, temperature, hypoglycemia, vital signs, and adverse

events. Patient agitation precluded baseline ECG recording before sedation. However, when possible, an ECG was obtained within 60 minutes of adequate sedation.

Outcome Measures

The primary outcomes were time to achieve adequate sedation for the first time (from administration of the study drugs to adequate sedation) and the proportion of patients adequately sedated at 5 and 10 minutes after study drug administration. Secondary outcomes were the need for additional parenteral sedative drugs to reach initial adequate sedation (ie, drugs in addition to the adjunct boluses and the initial midazolam dose), need for resedation within 60 minutes of initial adequate sedation, need for resedation from 60 minutes after initial adequate sedation until ED discharge, total midazolam dose administered in the 60 minutes after initial adequate sedation and from 60 minutes after initial adequate sedation until ED discharge, corrected QT interval (QTc), ED length of stay, and adverse events, including the need for airway management (jaw thrust, oral/nasal airway) or assisted ventilation (bag-valve-mask, intubation), oxygen desaturation (<90%), systolic blood pressure less than 90 mm Hg, dystonic reactions, seizures, vomiting or aspiration, and movement disorders.

Primary Data Analysis

The sample size was based on an earlier study in which 45% of patients in the control group (midazolam only) were adequately sedated at 5 minutes.[8] To demonstrate a proportion of 65% in the droperidol or olanzapine groups, at least 106 patients were needed in each group. Similarly, to increase the proportion of patients sedated at 10 minutes from 55% to 75%, 98 patients were needed in each group (α error .05, power 0.8). Hence, at least 318 patients were required overall. The study was not powered to compare adverse event rates or QTc intervals.

Data analysis was undertaken with Stata version 10 (StataCorp, College Station, TX). The intention-to-treat principle was used. The data on all patients who had been administered the study drugs were included in all analyses. This included data from patients with protocol violations and those whose group assignment was unblinded. Most data are presented descriptively, including graphically. Time to sedation was analyzed with difference in medians (95% confidence intervals [CIs]) and survival-time data and was plotted with a Kaplan-Meier curve. Hazard ratios (95% CI) were generated with the control group as a baseline reference. Patients who did not reach adequate sedation at all during their emergency stay were treated as censored observations for the hazard ratio calculations. Multivariable Cox's proportional hazards regression was used to investigate the effect of patients' regular medications (ie, benzodiazepines, selective serotonin reuptake inhibitors or serotonin noradrenaline reuptake inhibitor, atypical antipsychotics) on the hazard ratio.

Table 1. Baseline patient characteristics.

Characteristic	Study Group		
	Control,* n=115	Droperidol, n=112	Olanzapine, n=109
Age, median (IQR), y	35 (25–42)	32 (24–40)	34 (23–43)
Male, No. (%)	64 (55.7)	65 (58.0)	69 (63.3)
ATS category, No. (%)			
1. Resuscitation	11 (9.6)	11 (9.8)	6 (5.5)
2. Emergency	35 (30.4)	40 (35.7)	40 (36.7)
3. Urgent	62 (53.9)	49 (43.8)	58 (53.2)
4. Semiurgent	6 (5.2)	12 (10.7)	5 (4.6)
5. Nonurgent	1 (0.9)	0	0
Waiting time from triage to be seen by a physician, median (IQR), min	22 (5–51)	17 (7–66)	17 (6–40)
***ICD-10* category, No. (%)**			
Intoxication (drugs or alcohol)	32 (27.8)	34 (30.4)	35 (32.1)
Mental illness[†]	76 (66.1)	67 (59.8)	65 (59.6)
Organic illness[†]	7 (6.1)	11 (9.8)	9 (8.3)
Substance abuse history,[§] No. (%)	90 (78.3)	91 (81.3)	91 (83.5)
Usual medications, No. (%)[‖]	85 (73.9)	68 (60.7)	76 (69.7)
Benzodiazepines	35 (30.4)	20 (17.9)	33 (30.3)
SSRI or SNRI	31 (27.0)	25 (22.3)	27 (24.8)
Atypical antipsychotics	37 (32.2)	29 (25.9)	37 (33.9)
Depot antipsychotics	10 (8.7)	7 (6.3)	12 (11.0)
Conventional antipsychotics	1 (0.9)	4 (3.6)	4 (3.7)
Need for physical restraint, No. (%)	102 (88.7)	90 (80.4)	98 (89.9)
Sedatives prior enrollment,[¶] No. (%)	26 (22.6)	24 (21.4)	19 (17.4)
Police attendance on arrival, No. (%)	72 (62.6)	62 (55.4)	75 (68.8)
Mode of arrival, No. (%)			
Road ambulance	57 (49.6)	66 (58.9)	57 (52.3)
Police	49 (42.6)	32 (28.6)	40 (36.7)
Other[#]	9 (7.8)	14 (12.5)	12 (11.0)

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

*One patient with incomplete records for substance abuse history, regular medications, and use of sedative drugs before enrollment.

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

[†]Organic illness includes infections, delirium from an organic cause, and all other trauma.

[§]Substances include drugs or alcohol.

[‖]Relatively fewer patients in the droperidol group were receiving regular medications.

[¶]Sedatives (ie, benzodiazepines and antipsychotics) before study enrollment include 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, friends), public transport, and whether brought into ED by Good Samaritans.

RESULTS

Of 457 patients screened for eligibility, 121 were excluded and 336 were enrolled (Figure 1). All groups had similar baseline characteristics (Table 1). Patients with minor protocol

Table 2. Protocol violations.

Violation	Study Group		
	Control, n=115	Droperidol, n=112	Olanzapine, n=109
Protocol violations, No. (%)*	16 (13.9)	13 (11.6)†	14 (12.8)
Outside age (18–65 y)	1 (0.9)	1 (0.9)	2 (1.8)
Delay in initial midazolam dose‡	11 (9.6)	6 (5.4)	7 (6.4)
Initial midazolam dose omitted	3 (2.6)	4 (3.6)	3 (2.8)
Route of administration	0	1 (0.9)§	0
Dosing discrepancy	1 (0.9)‖	1 (0.9)¶	2 (1.8)#

*Forty-three protocol violations occurred among 42 patients.
†Two protocol violations occurred for 1 patient (old age and delay in immediate midazolam dosing).
‡Delay ranged from 6 minutes to a single extreme case of 105 minutes.
§Intramuscular route instead of intravenous.
‖Olanzapine/placebo-olanzapine 10 mg administered instead of 5 mg.
¶Olanzapine/placebo-olanzapine not administered.
#Olanzapine/placebo-olanzapine 10 mg administered instead of 5 mg.

Table 3. Primary endpoints, time to adequate sedation, and the proportion of patients sedated at specific points.

Variable	Study Group		
	Control, n=115	Droperidol, n=112	Olanzapine, n=109
Time to sedation, mean (SD), min	67.8 (197.5)	21.3 (97.1)	14.0 (33.3)
Time to sedation, median (IQR), min	10 (4–25)	6 (3–10)	5 (3–10)
Proportion sedated, No. (%), min			
At 5	31 (27.0)	40 (35.7)	39 (35.8)
At 10	56 (48.7)	74 (66.1)	74 (67.9)
At 30	90 (78.3)	103 (92.0)	98 (89.9)
At 60	100 (87.0)	106 (94.6)	104 (95.4)

violations (mainly delays in initial midazolam administration) were included in the analysis. The nature of the violations did not differ substantially between the groups (Table 2).

Adequate sedation could not be achieved in 5 patients (4 in the control group and 1 in the droperidol group) within the duration of their length of stay in the ED. Protocol violations did not occur in these patients.

The times to adequate sedation for the droperidol and olanzapine groups were significantly shorter than that for the control group (Table 3). The differences in medians for times to sedation between the control and droperidol and control and olanzapine groups were 4 minutes (95% CI 1 to 6 minutes) and 5 minutes (95% CI 1 to 6 minutes), respectively.

The proportions of patients sedated at 5 minutes after study drug administration were similar across the 3 groups (Table 3; Figure 2). However, at 10 minutes, there were significantly more sedated in the droperidol and olanzapine groups. At this time, the difference in proportions between the control and droperidol groups was 17.4% (95% CI 3.8% to 30.9%); between the control and olanzapine groups, 19.2% (95% CI 5.6% to 32.8%). Survival analysis showed a difference in the proportions of patients sedated at any point (Figure 2). Compared with the control group, patients in the droperidol and olanzapine groups were significantly more likely to be sedated. The hazard ratios were 1.61 (95% CI 1.23 to 2.11) and 1.66 (95% CI 1.27 to 2.17), respectively. Adjusting for

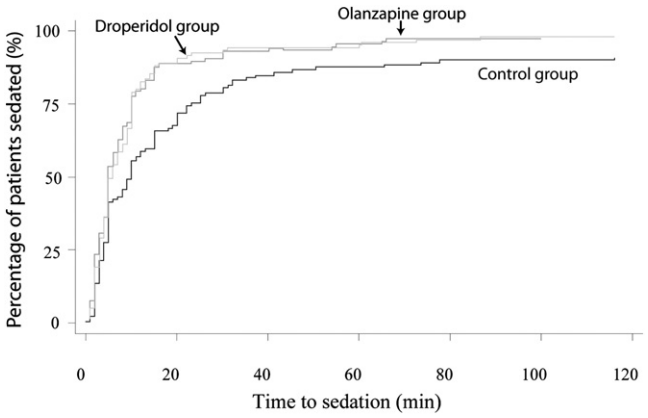


Figure 2. Kaplan-Meier curve comparing the proportion of patients sedated as a function of time.

Table 4. Secondary endpoints, the need for additional parenteral sedating drugs (patients may be administered more than 1 drug).

Variable	Study Group		
	Control,* n=115	Droperidol, n=112	Olanzapine, n=109
Need for additional parenteral sedating drugs to reach initial adequate sedation,† No. (%)	29 (25.2)	14 (12.5)	20 (18.4)
Midazolam	25 (21.7)	14 (12.5)	18 (16.5)
Droperidol	6 (5.2)	0	3 (2.8)
Olanzapine	6 (5.2)	0	4 (3.7)
Diazepam	0	0	2 (1.8)
Need for additional parenteral resedation in the 60 min after initial adequate sedation, No. (%)	42 (36.5)	26 (23.2)	25 (22.9)
Midazolam	41 (35.7)	25 (22.3)	23 (21.1)
Droperidol	3 (2.6)	1 (0.9)	3 (2.8)
Olanzapine	1 (0.9)	0	1 (0.9)
Haloperidol	0	0	1 (0.9)
Need for additional parenteral resedation from 60 min after initial adequate sedation until ED discharge, No. (%)	43 (37.4)	23 (20.5)	40 (36.7)
Midazolam	37 (32.2)	19 (17.0)	35 (32.1)
Droperidol	10 (8.7)	3 (2.7)	8 (7.3)
Olanzapine	15 (13.0)	5 (4.5)	12 (11.1)
Diazepam	1 (0.9)	0	2 (1.8)
Clonazepam	0	0	4 (3.7)
Haloperidol	1 (0.9)	1 (0.9)	1 (0.9)
Zuclopenthixol	1 (0.9)	0	2 (1.8)

*One patient with incomplete records for each of the 3 outcomes in this table.
†Additional parenteral sedating drugs include drug doses required in addition to the initial blinded study drug boluses and the initial dose of midazolam.

Table 5. Doses of parenteral sedating drugs administered postrandomization.

Doses	Study Group		
	Control,* n=115	Droperidol, n=112	Olanzapine, n=109
Initial immediate dose of midazolam[†]			
Initial dose omitted	3 (2.6)	4 (3.6)	3 (2.8)
IV 5 mg	93 (80.9)	87 (77.7)	96 (88.1)
IV 2.5 mg	19 (16.5)	21 (18.8)	10 (9.2)
Dose of midazolam, median (IQR), mg[†]			
Required to reach initial sedation	10 (5–15)	5 (2.5–5)	5 (5–10)
In the 60 min after initial adequate sedation	5 (5–10)	5 (2.5–7.5)	5 (5–7)
From 60 min after initial adequate sedation until ED discharge	10 (5–12)	5 (5–12.5)	10 (5–15)
Dose of droperidol, median (IQR), mg[†]			
Required to reach initial sedation	5 (5–5)	Nil	5 (5–10)
In the 60 min after initial adequate sedation	5 (2.5–5)	5 (5–5)	5 (5–10)
From 60 min after initial adequate sedation until ED discharge	6.25 (5–10)	2.5 (2.5–10)	6.25 (5–10)
Dose of olanzapine, median (IQR), mg[†]			
Required to reach initial sedation	10 (10–15)	Nil	10 (10–20)
In the 60 min after initial adequate sedation	10 (10–10)	Nil	10 (10–10)
From 60 min after initial adequate sedation until ED discharge	10 (10–10)	10 (10–10)	10 (10–15.5)

IV, Intravenous.
*One patient with incomplete records.
[†]Midazolam was inadvertently omitted or delayed in some patients. These were considered protocol violations and were analyzed accordingly. This table included patients administered the initial dose, including those with delays in administration.
[‡]Not inclusive of the initial doses administered.

Table 6. Reported adverse events.

Adverse Event	Study Group		
	Control, n=115	Droperidol, n=112	Olanzapine, n=109
Number of patients with reported events, No. (%)*	18 (15.7)	12 (10.7)	9 (8.3)
Airway obstruction[†]	5 (4.4)	3 (2.7)	3 (2.8)
Oxygen desaturation[†]	9 (7.8)	9 (8.0)	5 (4.6)[‡]
Hypotension[§]	6 (5.2)	4 (3.6)	3 (2.8)[‖]
Arrhythmia	1 (0.9)[¶]	0	1 (0.9)[‖]
Decreased GCS (score of 6)	1 (0.9)	0	0

GCS, Glasgow Coma Scale.
*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.
[‡]Patient was electively intubated 3 hours after initial adequate sedation for the purposes of obtaining a computed tomography scan (unrelated to the management of oxygen desaturation or ongoing agitation).
[§]All cases resolved after the administration of fluids, without sequelae.
[‖]Five minutes after initial sedation was achieved, a wide-complex bradycardia (50 beats/min), with hypotension (85/65 mm Hg) and a left bundle branch block was reported. The arrhythmia resolved spontaneously to sinus rhythm (90 beats/min during 15 minutes). The patient had consumed a large quantity of alcohol (blood alcohol concentration by breathalyzer 0.35%) and experienced drug intoxication (including heroin).
[¶]Patient with hyponatremia developed a narrow-complex supraventricular tachycardia (rate 180 to 200 beats/min with hypotension 87/67 mm Hg) 30 minutes after achieving adequate sedation. Arrhythmia and hypotension resolved with carotid sinus massage and normal saline solution. Irregular tachycardia developed 3 hours later (most likely atrial fibrillation) and reverted to sinus rhythm with magnesium chloride.

regular medications by multivariable Cox regression had negligible effect on the hazard ratios.

The groups did not differ in the proportion of patients who required additional parenteral sedating drugs to reach adequate sedation (Table 4). However, more patients in the control group required additional sedation in the 60 minutes after initial sedation and from 60 minutes after initial adequate sedation until ED discharge (Table 4). Of the 336 patients randomized to study drug allocation, 331 patients reached adequate sedation and were analyzed for the need for resedation at subsequent points (Table 4).

The groups did not differ in the initial dose of midazolam administered (Table 5). The control group required a slightly higher median cumulative dose of midazolam (10 mg) compared with the droperidol and olanzapine groups (5 mg) to achieve initial sedation.

The numbers of patients who experienced adverse events were similar among the groups, with 18 (15.7%), 12 (10.7%), and 9 (8.3%) reported in the control, droperidol, and olanzapine groups, respectively (Table 6). All events were readily and easily managed. The groups did not differ in median ED length of stay or disposition destination (Table 7). No patient was subsequently found to have a serious underlying medical illness.

An ECG was obtained within 60 minutes of initial adequate sedation for 211 (62.8%) patients: 62 (53.9%), 77 (68.8%), and 72 (66.1%) in the control, droperidol, and olanzapine groups, respectively. The median QTc intervals did not differ between groups: control 444 msec (interquartile range [IQR] 425 to 461 msec), droperidol 441 msec (IQR 421 to 460 msec), and olanzapine 448 msec (IQR 426 to 462 msec). Two patients had a QTc interval greater than or equal to 500 msec, 1 in the control group (500 msec) and 1 in the olanzapine group (512 msec). Neither patient experienced an adverse event related to the prolonged QTc. However, the patient in the control group experienced transient oxygen desaturation.

Twelve patients had their group allocation unblinded to guide ongoing management, including 6, 2, and 4 patients in the control,

Table 7. Comparison of ED length of stay and patient disposition.

Variable	Control, n=115	Droperidol, n=112	Olanzapine, n=109
ED length of stay, median (IQR), h	9.7 (5.7–14.7)	10.0 (6.7–13.2)	11.0 (7.2–14.7)
Patient disposition, No. (%)			
Home	56 (48.7)	63 (56.3)	58 (53.2)
ED observation ward	10 (8.7)	10 (8.9)	9 (8.3)
Psychiatry ward	33 (28.7)	20 (17.9)	25 (22.9)
Medical/other ward	10 (8.7)	8 (7.1)	9 (8.3)
Other institution ward*	5 (4.3)	7 (6.2)	6 (5.5)
Other facilities†	0	2 (1.8)	2 (1.8)
Null or absconded	1 (0.9)	2 (1.8)	0

*Other institutional wards include medical or psychiatry wards.
†Other facilities include correctional facilities, drug rehabilitation facilities, assisted accommodation (including nursing homes), and police.

Table 8. Reasons for unblinding study group allocation.

Reason	Control, n=115	Droperidol, n=112	Olanzapine, n=109
Number of patients with unblinding of group allocation, No. (%)	6 (5.2)	2 (1.8)	4 (3.7)
Reasons			
Sedation difficulty*	4 (3.5)	2 (1.8)	3 (2.8)
Patient required olanzapine	1 (0.9)	0	0
Inadvertent	1 (0.9)	0	0
Management by psychiatric service	0	0	1 (0.9)

*Difficulty in achieving or maintaining adequate sedation (eg, not sedated after administration of midazolam 20 mg).

droperidol, and olanzapine groups, respectively (Table 8). No group allocation was unblinded in response to adverse events.

LIMITATIONS

Selection bias may have occurred because not all suitable patients were enrolled. Enrollment may have been influenced by the physician's preference for other sedative drugs, study neglect, or excessive ED activity. However, the groups were well matched at baseline. Previous benzodiazepine exposure and tolerance are important potential variables. Regression analyses indicated that adjustment for regular medications did not affect the observed outcome measures. The greater number of control group patients transferred to psychiatry wards may imply more complex baseline morbidities. However, regardless of these, all patients were highly agitated on admission.

Although the sedation scale has been validated and widely used, its interpretation is potentially subject to observer bias because multiple observers were used to determine when the patients reached adequate sedation. It is likely this bias was evenly distributed across all groups. Bias was also likely minimized by blinding ED staff to group allocation. Furthermore, the scale cannot adequately assess oversedation.

Fewer ECGs were taken in the midazolam-only group, which may have been related to the relative difficulty in sedating patients in this group and the increased need for resedation. Consequently, this may have introduced selection bias affecting the median QTc for the treatment groups.

Although it is not known whether intravenous olanzapine 5 mg is equivalent to intravenous droperidol 5 mg, anecdotal evidence, current practice,[13] and this study suggest their effects are similar. Pharmacokinetic studies could be designed to evaluate intravenous olanzapine in the clinical setting. Such data may be useful to provide information on the equality of dosing between olanzapine and other parenteral sedating drugs to allow for fair comparisons in the clinical trial setting.

The question of antipsychotic (conventional or atypical) drug administration, alone or in combination, remains unresolved. It has been proposed that some benefits of combination therapies (eg, prevention or treatment of delirium) could be achieved with an antipsychotic agent alone.[32] In our study, the influence of midazolam on the sedation outcomes and adverse events in the olanzapine and droperidol groups cannot be easily separated. A clinical trial could be designed to compare the use of olanzapine alone with other sedating drugs to ascertain the clinical and adverse effects attributable to olanzapine alone.

Finally, in the ED setting, the intravenous route of drug administration is preferred because it allows dose titration and provides a more immediate onset of action.[33] However, the suitability of the intravenous route depends on the clinical setting and the resources available. Initial use of the intramuscular route may be appropriate if a patient cannot be physically restrained to enable an intravenous line to be safely established. However, oversedation is more common with intramuscular administration, and undersedation in some patients may ultimately require intravenous drug sedation.[33]

DISCUSSION

The principal finding of this study was that the drug combination regimens (droperidol-midazolam and olanzapine-midazolam) were significantly more efficacious than midazolam monotherapy in achieving rapid and adequate sedation. This is evidenced by shorter times to initial sedation, higher proportions of patients sedated at any point, and lower proportions requiring additional sedative drugs to reach initial sedation or for resedation (rescue drugs). Furthermore, the

adverse event profiles of the drug combinations were similar to that of midazolam alone, although the midazolam-only group had a slightly higher adverse event rate. These findings contribute to the limited published evidence in an area of medicine made difficult by the undifferentiated, unpredictable nature of the patients and the issues of informed consent.

The combination regimens appeared equally effective in this study. The proportions of patients requiring resedation in the 60 minutes after initial sedation were also similar. However, slightly fewer patients in the droperidol group required additional sedation to achieve initial sedation and considerably fewer required resedation from 60 minutes after initial sedation until ED discharge. This is likely attributable to droperidol's reported rapid onset of action when administered parenterally (3 to 10 minutes) and its known potent sedative effect.[15,34,35]

Combination therapy is believed to produce a rapid onset of sedation, lessen the requirement for resedation, and reduce benzodiazepine doses.[15] However, trials exploring the use of drug sedation in combination (in various clinical settings) have suffered methodological deficiencies, including uncontrolled drug redosing, lack of blinding, and settings other than the ED.[11,17,18,36,37]

To our knowledge, this is the first randomized, double-blind, clinical trial of acute agitation sedation comparing the use of intravenous sedative drug monotherapy with 2 drug combinations in the ED setting. It is also the first ED trial of intravenous olanzapine. The study involved highly agitated patients for whom management is difficult, and the attainment of informed patient consent was not feasible. Two thirds of patients were accompanied by police on arrival, and the majority required physical restraint to enable the administration of sedative drugs. This study addresses an important therapeutic area in which there are limited published data.

Earlier studies of droperidol monotherapy demonstrated a rapid onset and a longer duration of action compared with haloperidol[12] and lorazepam.[10] Rapid control of agitation with intramuscular droperidol has been demonstrated at 10, 15, and 30 minutes compared with intramuscular haloperidol.[12] Likewise, intravenous droperidol was superior to intravenous lorazepam in achieving sedation up to 60 minutes from the time of drug administration, despite similar sedation profiles at 5 minutes.[10] Isbister et al[9] also found that additional sedation was required more frequently in patients who received intramuscular midazolam 10 mg monotherapy, 62% versus 41% for the intramuscular midazolam 5 mg and droperidol 5 mg combination.[9] Similarly, Knott et al[8] reported that the proportion of patients requiring resedation within 60 minutes of initial sedation with intravenous midazolam was almost double that of patients receiving intravenous droperidol (18.9% versus 10.1%).

In 2001, a black box warning related to prolonged QT and torsades de pointes was applied to droperidol.[24] However, the evidence linking droperidol with prolonged QT, torsades de pointes, and sudden death is weak.[19] Debate around the evidence[19-23] has led to recommendations for additional clinical trials,[25] especially because droperidol remains in use in the ED setting.[7,13,26] Our findings do not support the Food and Drug Administration black box warning for droperidol because the droperidol group had a QTc similar to that of the other groups. Knott et al[4] also reported a similar median QTc in their droperidol group (439 msec, which was slightly higher than that of the midazolam group, 425 msec). However, firm conclusions cannot be made because the study was not powered to compare QTc intervals, not all patients had an ECG performed, and only single ECGs were performed.

Olanzapine is an effective atypical antipsychotic with a relatively benign adverse effect profile in the acute setting. Although intended for intramuscular administration, it is increasingly being used intravenously.[27,28] To our knowledge, before this study there were no published clinical trial data reporting the use of intravenous olanzapine. In our study, intravenous olanzapine appeared safe when used at the 5 mg dose and concurrently with other sedating drugs. The excipients in the olanzapine formulation (ie, lactose and tartaric acid) are safe for intravenous use, and the pH of the reconstituted olanzapine solution (5.55 to 5.63)[28] is within the acceptable range for intravenous administration (pH 3.0 to 10.5).[38]

No differences were observed between the study groups with respect to adverse events. The proportion of patients with adverse events in this study (15% of cases) was similar to that reported by Knott et al[8] (14%) and Isbister et al[9] (13%). However, the proportion of events observed in our midazolam-only group (19%) was lower than that reported by Isbister et al[9] (28%) and Spain et al[39] (31%). This is likely because of the larger initial dose of midazolam used in those studies.

No cases of phlebitis were reported and there were marginally fewer adverse events in the olanzapine group. It is, however, difficult to separate the influence of midazolam on the adverse events reported for this group. A larger study or safety registry is required to explore these infrequent adverse events.

Wilson et al[40] conducted a small retrospective study comparing the safety of intramuscular olanzapine (n=25) and haloperidol (n=71) in combination with benzodiazepines for the management of acute agitation in the ED. Contrary to an earlier report[41] and consistent with our current study, the combination of olanzapine-benzodiazepine was not associated with hypotension.

In summary, the administration of intravenous droperidol or olanzapine as a bolus adjunct to intravenous midazolam is efficacious and safe and provides more rapid sedation for acutely agitated patients in the ED compared with intravenous midazolam monotherapy. At the dose administered in this study (5 mg), intravenous droperidol does not appear to affect the QTc interval. Intravenous olanzapine appears safe and effective at the dose administered (5 mg) and in this setting. Future clinical trials could compare the use of olanzapine alone with other sedating

drugs to ascertain the clinical and adverse effects attributable to olanzapine alone.

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