Randomized Controlled Trial of Intramuscular Droperidol Versus Midazolam for Violence and Acute Behavioral Disturbance: The DORM Study

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Study objective: We determine whether droperidol, midazolam, or the combination is more effective for intramuscular sedation in violent and acute behavioral disturbance in the emergency department (ED).

Methods: We conducted a blinded randomized controlled trial of intramuscular sedation for violent and acute behavioral disturbance, comparing droperidol (10 mg), midazolam (10 mg), and droperidol (5 mg)/midazolam (5 mg). Inclusion criteria were patients requiring physical restraint and parenteral sedation. The primary outcome was the duration of the violent and acute behavioral disturbance, defined as the time security staff were required. Secondary outcomes included time until additional sedation was administered, staff and patient injuries, further episodes of violent and acute behavioral disturbance, and drug-related adverse effects.

Results: From 223 ED patients with violent and acute behavioral disturbance, 91 patients were included; 33 received droperidol, 29 received midazolam, and 29 received the combination. There was no difference in the median duration of the violent and acute behavioral disturbance: 20 minutes (interquartile range [IQR] 11 to 37 min) for droperidol, 24 minutes (IQR 13 to 35 minutes) for midazolam, and 25 minutes (IQR 15 to 38 minutes) for the combination. Additional sedation was required in 11 (33%; 95% confidence interval [CI] 19% to 52%) droperidol patients, 18 (62%; 95% CI 42% to 79%) midazolam patients, and 12 (41%; 95% CI 24% to 61%) in the combination group. The hazard ratio for additional sedation in the midazolam versus droperidol group was 2.31 (95% credible interval 1.01 to 4.71); for the combination versus droperidol, 1.18 (95% credible interval 0.46 to 2.50). Patient and staff injuries and number of further episodes of violent and acute behavioral disturbance did not differ between groups. There were two adverse effects for droperidol (6%; 95% CI 1% to 22%), 8 for midazolam (28%; 95% CI 13% to 47%), and 2 for the combination (7%; 95% CI 1% to 24%). An abnormal QT occurred in 2 of 31 (6%; 95% CI 1% to 23%) droperidol patients, which was not different from the other groups.

Conclusion: Intramuscular droperidol and midazolam resulted in a similar duration of violent and acute behavioral disturbance, but more additional sedation was required with midazolam. Midazolam caused more adverse effects because of oversedation, and there was no evidence of QT prolongation associated with droperidol compared with midazolam. [Ann Emerg Med. 2010;56:392-401.]

Please see page 393 for the Editor's Capsule Summary of this article.

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INTRODUCTION

Background

Violence and aggression in the emergency department (ED) is a difficult and dangerous problem that can result in harm to the patient or staff. The majority of cases are due to acute delirium from alcohol intoxication, are due to psychostimulant toxicity, or are associated with deliberate self-harm and drug overdose.[1,2] Many of these patients will not respond to verbal de-escalation or accept oral medications, and some arrive in police custody already restrained. To allow the safe assessment, diagnosis, and treatment of these patients, parenteral sedation and physical restraint are usually required.

There is ongoing controversy about the safest and most effective medications for sedation of violence and acute behavioral disturbance in the ED.[3] There is no type of medication that provides sedation in all patients with no adverse

Editor's Capsule Summary

What is already known on this topic

Droperidol, once widely used in the United States, is now less commonly used because of a black box Food and Drug Administration warning.

What question this study addressed

What is the most effective intramuscular medication for sedation in agitated patients, midazolam, droperidol, or a combination of both medications, and is there a difference in adverse events between groups?

What this study adds to our knowledge

In this 91-patient randomized controlled trial conducted in Australia, there were no differences in time to sedation with any of the medications, but patients who received droperidol required less additional sedation.

How this is relevant to clinical practice

Although this study is too small to establish the safety of droperidol, it confirms that it is an effective agent and provides no evidence that it is not safe.

effects. Currently, the 2 major groups of medications used are benzodiazepines (midazolam, diazepam, and lorazepam) and antipsychotics (haloperidol, droperidol, and olanzapine). There is increasing evidence that the benzodiazepines fail to sedate a proportion of these patients because of benzodiazepine tolerance, and when larger doses are used a proportion are oversedated.[4] Antipsychotics have been associated with cardiac dysrhythmias and QT prolongation,[5,6] and some are only mildly sedating, such as haloperidol.

Droperidol is a highly sedative antipsychotic that was widely used until the Food and Drug Administration in the United States issued a black box warning in 2001 because of concerns about QT prolongation and torsades des pointes. This was based on little evidence[7] and an unusual number of spontaneous reports on 1 day, mainly from outside the United States.[8] A systematic review of droperidol use failed to support a strong association with QT prolongation and torsades des pointes,[7] and droperidol was not found to be commonly associated with torsades des pointes in a systematic review of torsades des pointes cases.[9] However, the use of droperidol has fallen out of favor since the black box warning despite decades of its effective use in EDs and psychiatric units around the world.[10,11] Few controlled trials have been reported assessing its effectiveness for sedation and safety compared with that of other agents in the ED.

Importance

There is limited information about the intramuscular route for sedative drugs in violent and acute behavioral disturbance,[2] which is often the only possible route of administration for these patients. Intravenous sedation requires increased staffing; otherwise, it is effectively impossible and potentially dangerous to attempt to gain intravenous access. There is a real risk of needlestick injuries or other physical injuries to the staff, and most guidelines suggest intramuscular sedation in this setting. Antipsychotic medications such as droperidol are an option to benzodiazepines for intramuscular sedation, but there are few studies comparing intramuscular benzodiazepines with antipsychotics. To our knowledge, there is only 1 trial of intramuscular droperidol that compared it with midazolam and ziprasidone.[2] This showed that droperidol was at least as effective as midazolam, whereas midazolam required more rescue sedation. Studies of intravenous droperidol suggest it has a longer duration of action compared with that of benzodiazepines[2,12] but potentially a slower onset of action.[13] All of these previous trials have used low doses, with many patients requiring further sedation. No previous trial has investigated the combination of intramuscular benzodiazepines and droperidol.

Goals of This Investigation

This study aimed to determine whether intramuscular droperidol, midazolam, or the combination results in a shorter duration of the violent and acute behavioral disturbance episode defined by the time security staff are required. In addition, the study aimed to determine for each drug treatment the requirement for additional sedation, staff and patient injuries, further episodes of violent and acute behavioral disturbance, and drug-related adverse effects, including the occurrence of QT prolongation with droperidol.

MATERIALS AND METHODS

Study Design and Setting

We undertook a blinded randomized controlled trial of intramuscular droperidol versus midazolam versus a combination of both for the sedation of violent and acute behavioral disturbance in the ED. The patients, the health care providers, and the investigators were blinded to the treatment arms. The primary outcome was the duration of the violent and acute behavioral disturbance.

The study was undertaken from August 2008 to July 2009 in a hospital with a large number of patients who had violent and acute behavioral disturbance and presented to the ED. It is an urban ED with 27,000 annual presentations, with approximately 5.2 per 1,000 with violent and acute behavioral disturbance.[1] The hospital has a tertiary clinical toxicology and liaison psychiatry service, as well as a medical inpatient drug and alcohol unit. Ethics approval was obtained from the regional Human Research Ethics Committee. Consent was waived because of the requirement for immediate treatment and patients' inability to consent to a research study in the setting of medical treatment being given as a duty of care. The trial was registered with the Australian Clinical Trial Registry.

Selection of Participants

Patients (aged 18 years or older) were eligible for inclusion if they presented at any time (24 hours a day, 7 days a week) to the ED with violent and acute behavioral disturbance and required both physical restraint and parenteral sedation according to the assessment of the ED nursing or medical staff. Initially, we intended to study patients only with psychostimulant toxicity, but because it was impossible to establish the cause on presentation and it rapidly became apparent that psychostimulant toxicity was uncommon, all patients with violent and acute behavioral disturbance were included irrespective of cause.

The exclusion criteria were successful verbal de-escalation or de-escalation when confronted by the security team ("show of force"), agreement to oral or intravenous sedation, other sedative medication already administered or patient did not remain in the ED (absconded, escorted off premises by police), and acute seizures/postictal.

Interventions

After patients were identified for recruitment, one of the investigators or a paid on-call research assistant was contacted before or as the trial drug was given. The research staff recorded all information for the study and obtained ECGs for all cases. A dose of 10 mg was chosen for the study according to a previous study of sedation with midazolam, in which an initial dose of 10 mg was used.[4] An equivalent dose of droperidol was then based on previous comparisons of midazolam and droperidol.[2,13] Randomized prepacked trial drugs were available in multiple locations in the ED and were administered by the clinical staff for intramuscular sedation. The trial drug(s) consisted of 2 vials randomized to contain 10 mg droperidol (2×5 mg vials), 10 mg midazolam (2×5 mg vials), or 5 mg droperidol (1×5 mg vial)+5 mg midazolam (1×5 mg vial).

Vials of droperidol (5 mg) and midazolam (5 mg) were purchased from Phebra, Ltd. (New South Wales, Australia) and Sandoz, Ltd. (New South Wales, Australia), respectively. The active drugs were transferred to identical vials in equal volumes under aseptic conditions at Stenlakes Pharmacy, Sydney, Australia. Identical vials of 5 mg of each drug were randomized and packed by the hospital pharmacy in blocks of 6 or 9 (eg, ABCABC, AABCCABCB) and numbered sequentially. Random blocks of 6 or 9 study codes with allocation to the 3 groups (A, B, or C) were computer generated and supplied directly to the hospital pharmacy. Trial drugs were used in sequence order.

All patients recruited were treated in a critical care area with continuous cardiac monitoring, pulse oximetry, and noninvasive blood pressure monitoring for the 6 hours unless they absconded or were alert and no longer requiring restraint. All equipment necessary for resuscitation was available at the bedside. It is standard practice in the ED not to administer oxygen routinely to patients who are sedated because of the risk of disguising hypoventilation. The 2 vials of the trial drug(s) were administered as intramuscular injections to each thigh/gluteal region or deltoid if this was the only site accessible. Any further sedation given was at the discretion of the treating physician.

Any major adverse effect (respiratory depression requiring intubation, arrhythmias including torsades des pointes, extrapyramidal adverse effects requiring administration of benztropine, anaphylaxis, or any other major serious unexpected effect) was to be reviewed by the investigators and a report was to be supplied to the ethics committee. In the event of 2 similar major adverse effects occurring, the trial would be temporarily stopped and the cases reviewed by an external clinical pharmacologist with unblinded treatment allocation available. According to this review and a decision by the investigators, the trial could be terminated.

Data Collection and Processing

All data were recorded on clinical research forms, which were then entered into a relational database (Microsoft Access; Microsoft Corp., Redmond, WA). Observations were done every 5 minutes for the first 30 minutes and then every 15 minutes for the next 90 minutes and then hourly until study completion 6 hours after administration of the trial drug(s). Observations included pulse rate, blood pressure, oxygen saturations, respiratory rate, and the Altered Mental Status Scale (see Table E1,[2] available online at http://www.annemergmed.com). The Altered Mental Status Scale evaluates both agitation and sedation on the same scale, with scores from −4 to +4. It is a modification of the Behavioral Activity Rating Scale[14] and has been previously used in this patient group.[2,15] All research staff and emergency nursing staff were given training on the Altered Mental Status Scale. The Altered Mental Status Scale was recorded by the research staff, except for the initial scores done by the clinical staff.

All patients (when practical) received an ECG 30 minutes, 1 hour, and 4 hours after receiving the trial drug(s). ECGs were not possible before the administration of sedative medication because of the patients' agitation. The time and dose of any further medications were recorded. The decision to administer additional sedation, as well as the type of drug, timing, and dose, was made by the treating physician. However, because of the use of intramuscular sedation they were encouraged to wait at least 10 minutes after study drug administration before administering additional sedation. Adverse drug effects and patient and staff injuries were recorded. Urine drug screens and blood or breath alcohol levels were requested for all patients when possible.

Outcome Measures

The primary outcome was defined as the duration of the violent and acute behavioral disturbance episode, taken as the time that the security staff were required to be present on the first occasion with the patient as part of a standard hospital team approach to violent and acute behavioral disturbance episodes.[1] All activations of the security staff occur through the hospital switchboard and are recorded in the security log. The duration

of the violent and acute behavioral disturbance episode was therefore taken from the security log as the time from the initial call for security until the "all clear" time when the security officers are released from attendance. An "all clear" is called when the patient is restrained safely, the patient is sedated or settling, and any verbal abuse is decreasing or has ceased. An "all clear" is decided in consultation with the clinical staff. None of the security, emergency medical, or nursing staff were informed that this was one of the primary outcomes for the study. The primary outcome was derived from the routine management of violent and acute behavioral disturbance and not measured or influenced by the investigators or research staff.

The secondary outcomes were the time until additional sedative medication was administered within the 6-hour study period, reduction in the Altered Mental Status Scale by 3 points or to a score of 0 or less 20 minutes after trial drug(s) administration, injuries to the patient or staff, further calls to security for assistance, and any drug-related adverse effect (oxygen desaturation [<90%], airway obstruction requiring intervention, tracheal intubation, cardiac arrhythmias, prolonged QT interval, hypotension, extrapyramidal side effects, akathisia, and anaphylaxis).

The effect of the trial drug(s) on the QT interval was analyzed because of reports of droperidol affecting the QT interval. The QT interval was manually measured on all 12-lead ECGs, using a previously developed method.[16] The QT interval was measured from the start of the Q wave to the point where the T wave returns to baseline (isoelectric line) in 3 chest leads and 3 limb leads, and the median was calculated.[16] HR was taken from the ECG machine's automated readout. The QT was measured for all ECGs before unblinding of the data. The QT-HR pairs for each ECG were plotted on a previously validated QT nomogram to determine whether any of the ECGs had an abnormal QT-HR pair.[9] The proportion of instances with an abnormal QT was compared across the 3 groups.

Primary Data Analysis

The sample size was based on an estimated within-group SD of 10 minutes' duration of violent and acute behavioral disturbance before commencement of the study and detection of a difference in the mean duration of 10 minutes. Twenty-three patients were required in each arm of the study (α=.05, β=.2) after adjusting for multiple comparison when comparing 3 means (ANOVA). The estimates of the within-group SD were taken from a month of security logs and may have underestimated this. Given that, to our knowledge, no previous studies had measured the duration of violent and acute behavioral disturbance or requirement for security personnel, a 10-minute difference in mean duration was determined by the investigators as clinically important. No interim analysis was planned, and according to the expectation of 70 to 100 patients being eligible during a 1-year period,[1] the study was undertaken and funded for 1 year. Because of the possibility of the within-group SD being underestimated, the study was continued for the full year of funding, rather than recruitment of only 23 patients to each arm.

Continuous variables are presented as medians with interquartile ranges (IQR) for ease of interpretation, and proportions are presented with 95% confidence intervals (CIs). Analysis of the primary outcome was intention to treat, the 3 continuous outcomes were compared with the Kruskal-Wallis test, and $P \leq .05$ was regarded as statistically significant.

A time to event analysis was undertaken to compare the times until additional sedation was required for each of the 3 groups. The times to additional sedation were assumed to follow a Weibull distribution because of the changing hazard over time, and each treatment group was included as a categorical covariate in the model. Age, sex, and alcohol consumption were included as potential covariates in models. Both a naive model, where independent parameters were estimated for each of the 3 treatment groups, and an interaction model, which allowed the combined droperidol/midazolam treatment group to have a synergistic, antagonistic, or additive effect, were tried. Patients who did not receive further sedation were right censored at 6 hours when the study finished. Goodness of fit of the model was investigated by comparing predicted times to further sedation simulated from the model with Kaplan-Meier plots of the observed times. Hazard ratios and 95% credible intervals of the hazard ratios were calculated for midazolam alone and droperidol/midazolam, with droperidol alone as the reference. In addition, we estimated the probability that hazard ratio was greater than 1.0 (ie, increased hazard of additional sedation). Analyses of the secondary outcomes were descriptive and presented as proportions with 95% CIs. Plots were made of the median and IQR of the Altered Mental Status Scale scores versus time to provide a visual representation of the sedative effects of each treatment group.

All analyses and graphs were made with GraphPad Prism version 5.03 for Windows (GraphPad Software, San Diego, CA; http://www.graphpad.com), except for the time to event analysis, which was carried out in WinBUGS 1.4.3 (http:www.mrc-bsu.cam.ac.uk/bugs/).[17] Further details of the time to event analysis and the fully Bayesian analysis with WinBUGS are provided elsewhere.[18–20]

RESULTS

There were 223 ED patient presentations with violence and acute behavioral disturbance during the 1-year study period. Of these, 121 were excluded and a further 11 were missed (Figure 1), resulting in 91 patient presentations being included. All 91 presentations received the trial medication and had data collected for at least 90 minutes, and 79 presentations remained in the ED until the completion of the trial at 6 hours. Of 79 patients involved, 69 presented on 1 occasion, 8 presented on 2 occasions, and 2 presented on 3 occasions. Of the 91 patient presentations, 33 patients received droperidol alone, 29 received midazolam alone, and 29 received the combination. The 3 treatment groups had similar baseline characteristics (Table 1), except that there were more men in the midazolam and

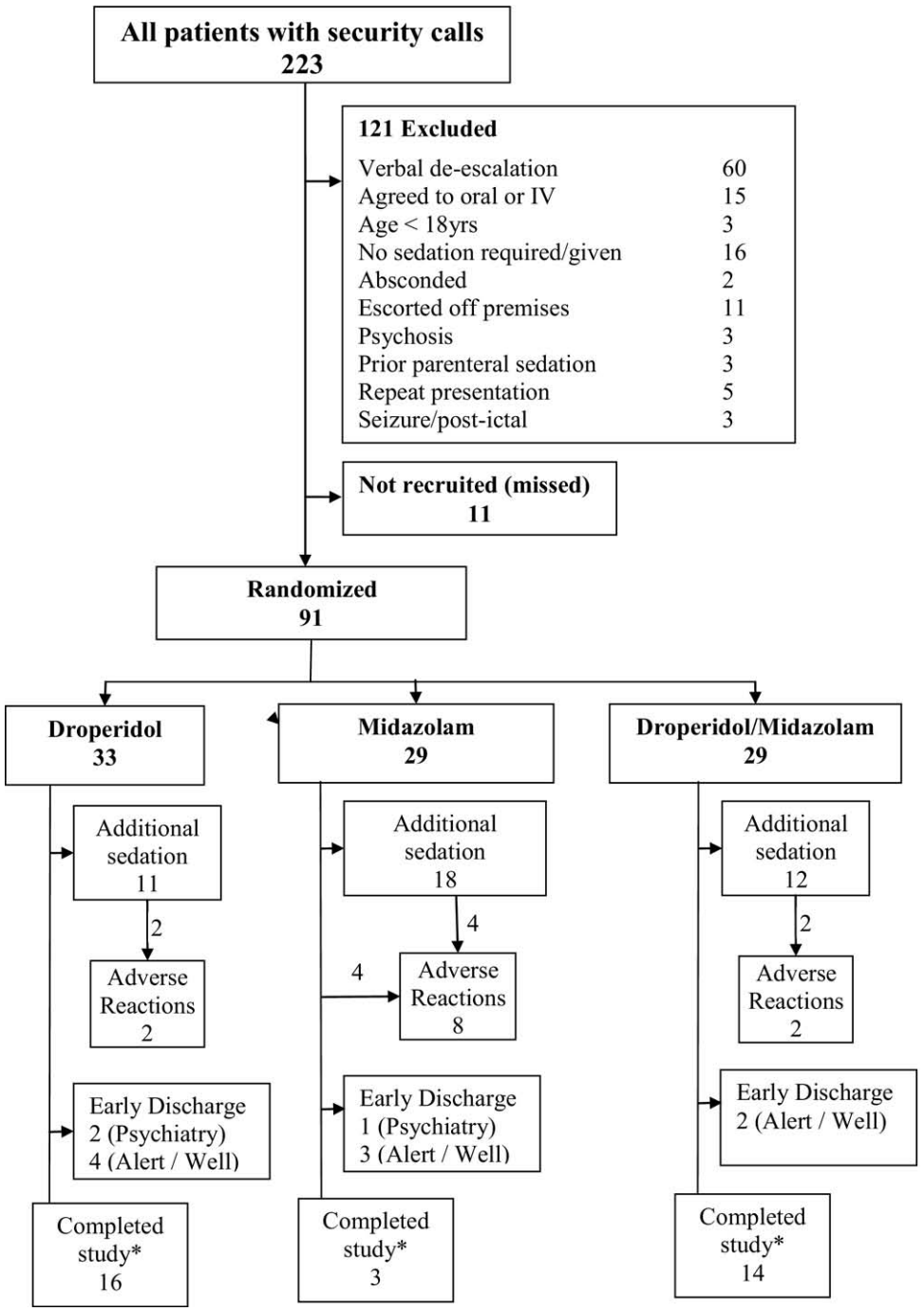

Figure 1. Flow chart for all patients with a violent and acute behavioral disturbance recorded in the security log and who were recruited to the trial. It shows the flow of the patients with their allocation, whether they received additional sedation, whether they experienced an adverse effect, and whether they completed the study. The final box includes patients who completed the study with only the study drug for sedation and no adverse effects. *IV*, Intravenous.

combined groups. Figure 1 shows the flow of patients, including those who required no additional sedation and had no drug-related adverse effects, which can be regarded as uncomplicated sedation. Twelve patients were discharged before the 6-hour study period because they were transferred to psychiatry (3 patients) or awoke from sedation with no evidence of delirium, agitation, or aggression and were reassessed and discharged by the clinical staff (9 patients).

The median duration of violent and acute behavioral disturbance was 20 minutes (IQR 11 to 37 minutes) for droperidol alone, 24 minutes (IQR 13 to 35 minutes) for midazolam alone, and 25 minutes (IQR 15 to 38 minutes) for

Table 1. A comparison of the baseline characteristics for the 3 treatment groups.

	Droperidol (10 mg)	Midazolam (10 mg)	Droperidol (5 mg) +Midazolam (5 mg)
Number of presentations	33	29	29
Age, y, median, (IQR)	37 (25–45)	35 (27–43)	30 (22–40)
Sex, male, No. (%)	12 (36)	18 (62)	15 (52)
Clinical assessment of agitation, No. (%)			
Alcohol intoxication	23 (70)	22 (76)	19 (66)
Deliberate self-harm	16 (48)	12 (41)	9 (45)
Drug-induced delirium	2 (6)	3 (10)	3 (10)
Acute psychosis	2 (6)	1 (3)	2 (6)
Other	1 (3)	0	1 (3)

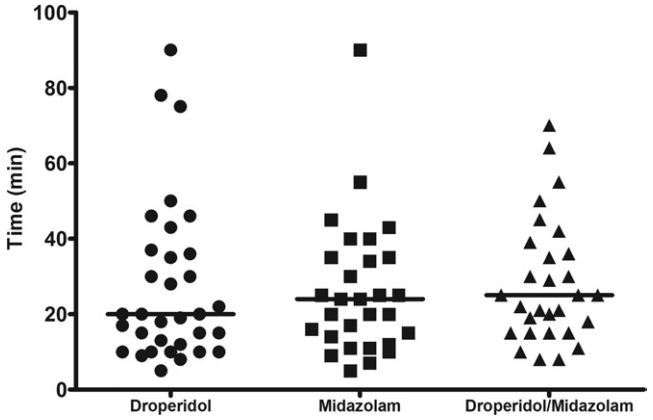

Figure 2. Scatterplots showing the duration of the violent and acute behavioral disturbance, comparing the 3 groups of patients in the randomized controlled trial. The horizontal lines are the median of the data.

the combination; these are not significantly different (P=.66) (Figure 2).

A comparison of the secondary outcomes is presented in Table 2. The time to additional sedation is shown in Kaplan-Meier plots (Figure 3), and the time to event model that best described the data was an interaction model for the treatment arms and inclusion of age as a covariate. Sex or alcohol ingestion was not a significant covariate in the model. The hazard ratio for additional sedative medication for midazolam versus droperidol was 2.31 (95% credible interval 1.01 to 4.71), and the posterior probability that this hazard ratio was greater than 1.0 was 0.98. The hazard ratio for the droperidol/midazolam combination versus droperidol was 1.18 (95% credible interval 0.46 to 2.50), with a posterior probability that the hazard ratio was greater than 1.0 of 0.56. The hazard ratio for additional sedative medication for an increment of 10 years in age was 0.68 (95% credible interval 0.51 to 0.89), with a posterior probability that the hazard ratio was less than 1.0 of 0.999.

Altered Mental Status Scale scores provided information on level of sedation over time for the 3 groups (Figure 4). Droperidol produced more consistent moderate sedation compared with highly variable and unpredictable sedation, including deeper sedation with midazolam or the combination. There was only 1 patient injury, which was a fractured wrist in a patient with a recent open reduction and internal fixation for a previous injury. Staff injuries occurred with similar frequency between groups (Table 2).

Drug-related adverse effects were more common in the midazolam group (Table 2), and all sedative-related adverse effects in the droperidol and combination group occurred after additional sedation was given, including 3 of the 4 immediately after administration of intravenous benzodiazepines (Table 3). Figure 5 provides a breakdown of cases by treatment arm, as well as by whether patients were intoxicated with alcohol or received additional benzodiazepine sedation in the first hour, showing how many of the total in each of the 12 groups had an adverse effect. This suggests that adverse effects, in addition to being more common after midazolam treatment, were associated with alcohol intoxication and benzodiazepine additional sedation (droperidol group).

An ECG was done within 4 hours in 90 of the 91 presentations. Of these 90, one patient had preexisting atrial fibrillation and one had preexisting right bundle branch block and were excluded from the QT analysis. Of the remaining 88 patients, 54 had all 3 ECGs recorded. Abnormal QT-HR pairs occurred in 2 of 31 patients from the droperidol group, 2 of 29 from the midazolam group, and 4 of 29 from the droperidol/midazolam group.

LIMITATIONS

A concern with any study of sedative medications in this patient population is the possibility of interaction between the drugs being administered in the trial and any drugs or alcohol that the patients have already ingested. For example, patients intoxicated with alcohol may be more likely to become oversedated with benzodiazepines. Figure 5 is an attempt to address this issue. It suggests that alcohol is associated with a larger number of adverse effects, and this appears to be mainly with the concomitant administration of benzodiazepines (ie, the trial drug in the midazolam alone arm and additional benzodiazepine administration in the droperidol arm). It is this very interaction between alcohol and midazolam that is likely to result in oversedation, and rather than this being "confounding," it is in fact an important result for this patient group: midazolam is associated with more respiratory depression in a patient group in which alcohol intoxication is common.

Random allocation aims to ensure that factors that may influence the sedative effects of the drugs are balanced across the groups. Table 1 shows that there were similar numbers of patients with alcohol and drug intoxication in each of the 3 groups. This may have been improved by stratifying patients who were alcohol intoxicated but would require accurate information on the cause of the agitation at randomization, which is rarely possible. The role of these interacting factors cannot be ignored, and the results of this trial should be applied

Table 2. Secondary outcomes for the 3 groups in the study.*

	Droperidol		Midazolam		Droperidol/Midazolam	
	No.	Proportion, % (95% CI)	No.	Proportion, % (95% CI)	No.	Proportion, % (95% CI)
Additional sedation required	11	33 (19–52)	18	62 (42–79)	12	41 (24–61)
Sedated at 20 min (AMSS≤0)	24	73 (54–86)	15	52 (33–70)	23	79 (60–91)
Additional security attendances	2	6 (1–22)	6	21 (9–40)	4	14 (5–33)
Staff injuries	3	9 (2–25)	1	3 (0–20)	2	7 (1–24)
Drug-related adverse effects	2	6 (1–22)	8	28 (13–47)	2	7 (1–24)
Abnormal QT interval	2†	6 (1–23)	2	7 (1–24)	4	14 (5–33)

AMSS, Altered Mental Status Scale.
*Reported as absolute numbers.
†Only 31 of the 33 patients had ECG results available.

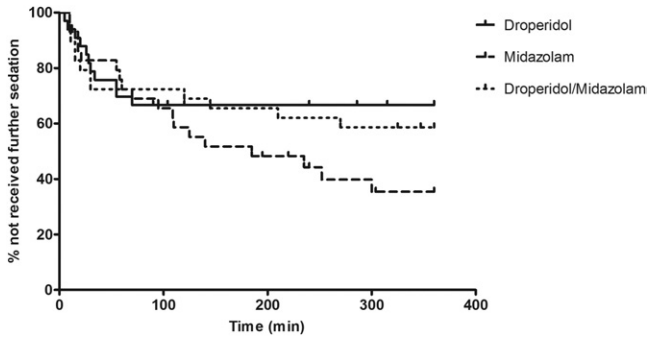

Figure 3. Kaplan-Meier plots comparing the proportion of patients who received further sedation as a function of time for the 3 groups.

with caution outside of the population of ED patients with violent and acute behavioral disturbance.

Another limitation was that the medications in the study were not dosed according to patient weight, which may have contributed to adverse effects in smaller patients or poor effectiveness in larger patients. Obtaining an accurate patient weight before drug administration in this patient group is practically impossible because a patient must be cooperative. More important, even if weight-based dosing had been used in the study it would be difficult to reproduce in clinical practice. For example, if weight-based dosing improved the predictability in the Altered Mental Status Scale scores with midazolam compared with droperidol, this would mean that midazolam should be used only if patient weight is known. If this were the case, then the study would suggest that midazolam is problematic in this patient group unless weight is known.

One criticism of the outcomes is that the duration of the violent and acute behavioral disturbance was used as the primary outcome rather than the time until sedation according to a sedation scale such as the Altered Mental Status Scale. The investigators chose the duration of violent and acute behavioral disturbance because in the institution where the study was conducted, the length of time that security personnel attend a patient in the hospital is recorded for legal and administrative purposes. It was believed that this was a more objective measure than using a sedation scale and more clinically applicable because it measured the duration of the violent and acute behavioral disturbance and the effect that the episode had on the ED. However, analysis of the Altered Mental Status Scale provided unique insight into the onset, variability, and duration of sedation (Figure 4) and may have been a better primary outcome.

The Altered Mental Status Scale was recorded by the research staff, except when the researchers were not immediately available, so in some cases initial scores were recorded by the clinical staff. There may have been minor interobserver differences in the use of the Altered Mental Status Scale because it was not possible for a single researcher to enroll and record data on every patient. However, the Altered Mental Status Scale was a secondary outcome and used mainly as a simple clinically useful score to assist in the management of the patients.

Allowing the administration of additional sedation to be at the discretion of the treating physician meant that this outcome provided some indication of whether the patient required further sedation according to the treating clinician's assessment. Such unstructured administration of further sedation meant that it may have influenced the occurrence of adverse effects. However, we believed it was still important to initially provide a comparison of the adverse effects without considering such influences because this was unlikely to be biased by our knowledge of group allocation. After this, we examined each drug-related adverse effect in relation to the timing, drug, and dose of any additional sedation (Table 3). This analysis further supports midazolam's being associated with a higher probability of an adverse event. Only in the midazolam group did adverse effects occur when no additional medication was administered.

DISCUSSION

This study shows that intramuscular droperidol is effective and safe for the sedation of violence and acute behavioral disturbance in the ED. In comparison with intramuscular midazolam, droperidol resulted in a similar security-duration requirement, required less additional sedation, and had a lower rate of adverse effects. Most revealing was the predictable response to droperidol according to the Altered Mental Status Scale, with rapid and then persistent sedation but not oversedation (Figure 4). The combination of droperidol/

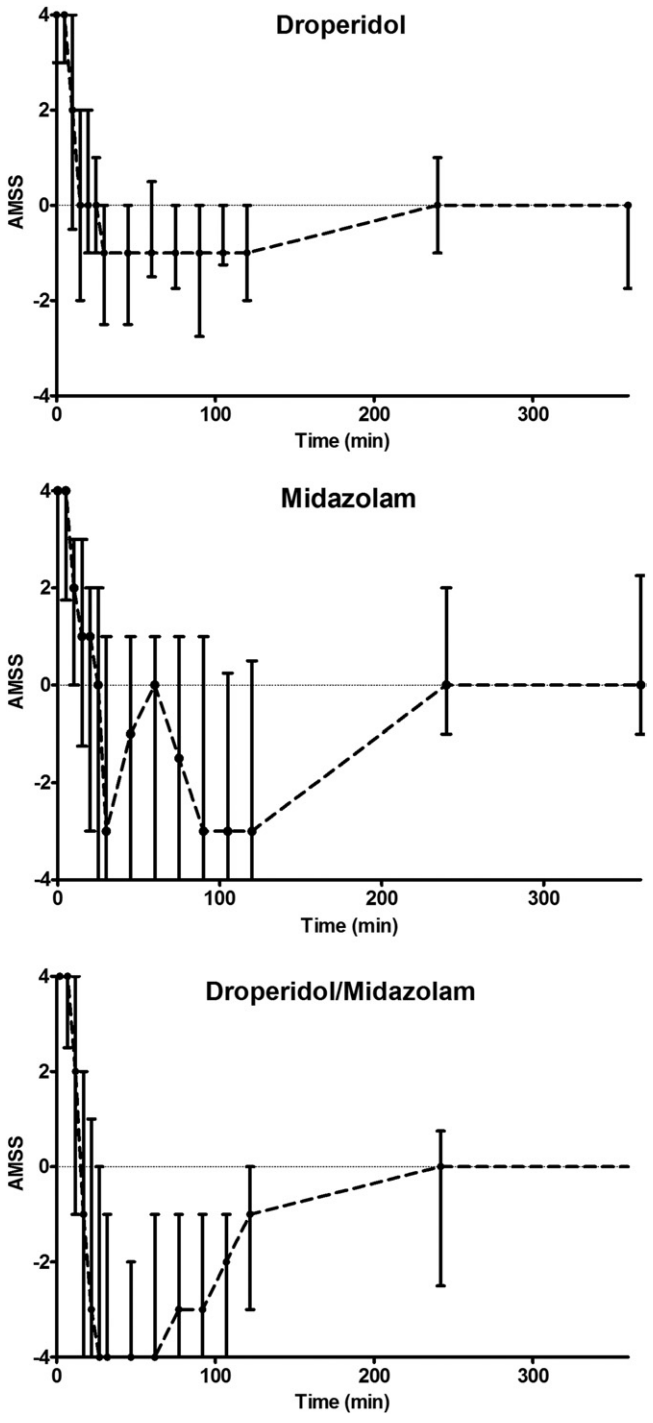

Figure 4. Plots of the median AMSS versus time for droperidol (top panel), midazolam (middle panel), and the droperidol/midazolam combination (bottom panel). Error bars show the IQR of the AMSS at each time point.

midazolam caused deeper and more unpredictable sedation according to the Altered Mental Status Scale (Figure 4). The most concerning finding of the study was the unacceptably high rate of adverse reactions in more than a quarter of patients receiving intramuscular midazolam. Droperidol caused no arrhythmias or QT prolongation.

There has been significant concern about the risks of droperidol, particularly in relation to QT prolongation and torsades des pointes.[21,22] However, there is limited evidence to support this stance,[7,8,10,11] and prospective reevaluation of the safety of droperidol is justified for a drug that was used safely in large numbers of patients for decades.[10,11] In this study, we collected between 1 and 3 ECGs after droperidol administration, including 3 ECGs in 60% of cases. There was no significant difference in abnormal QT intervals across the 3 arms of the study. However, the overall proportion of abnormal QT intervals in the study was higher than that in the normal population.[9] This high rate of abnormal QT interval is likely to be due to a combination of preexisting illness in these patients and in some cases drugs ingested before sedation. In this setting, the therapeutic use of droperidol for sedation appears to be relatively safe, although larger studies using continuous 12-lead Holter monitoring will be important.

Potentially a more important finding in this study was the unpredictable effect of intramuscular midazolam, which caused both oversedation, with more sedative-related adverse effects, and undersedation, with a greater requirement for additional sedation, as illustrated in Figure 5. Figure 4 also supports this finding, with a much more erratic median Altered Mental Status Scale over time for midazolam compared with droperidol and a large interpatient variability in the scores at each time point, the IQR crossing an Altered Mental Status Scale score of zero at all time points. The unpredictable response to intramuscular midazolam is most likely due to differences in individual patient tolerance and is particularly important in patients with violent and acute behavioral disturbance who have an increased use of drugs and alcohol. This makes intramuscular midazolam, at least, and potentially other benzodiazepines, a problematic choice of drug in a setting in which rapid sedation is required, usually with little knowledge of the patient.

Although no patients required tracheal intubation and ventilation, the patients who had either airway obstruction or desaturation received immediate attention because of the presence of a dedicated clinical researcher. However, this may not always be possible in a busy ED, and these patients may develop more significant sequelae. Previous studies support this high rate of adverse effects with midazolam, especially for the larger dose of 10 mg,[2,4,13,23] particularly with intramuscular use. One study by Martel et al[23] reported a significant increase in sedative adverse effects when droperidol was discontinued for out-of-hospital sedation, which was most likely due to the need to then use benzodiazepines in the out-of-hospital setting.

The combination of droperidol/midazolam was originally included in an attempt to gain the potential benefit of more rapid onset of action with midazolam and the longer duration of action with droperidol.[2,13] However, the onset of action of droperidol alone was similar to that of the combination and midazolam alone, so there appeared to be little benefit with the

Table 3. Description of all adverse drug reactions that occurred for each arm of the study, including the time of the reaction and the time and type of any additional sedation that was administered.

	Adverse Event		Additional Sedation		Blood Alcohol Level
Study Drug	**Type of Reaction**	**Time (Min)***	**Time (Min)***	**Drug and Dose**	
Droperidol	Desaturation	22	20	10 mg IV diazepam	Nil
Droperidol	Desaturation	80	80	5 mg IV midazolam	0.3
Midazolam	Desaturation/airway obstruction	20	12 and 18	5 mg IV droperidol (×2)	0.01
Midazolam	Desaturation	65	55	5 mg IV droperidol	0.4
Midazolam	Desaturation	35	18	5 mg IV droperidol	0.26
Midazolam	Airway obstruction	24	Nil	—	0.18
Midazolam	Desaturation (93%)/hypotension	10	Nil	—	0.25
Midazolam	Desaturation	35	Nil	—	0.34
Midazolam	Desaturation	70	140	(5 mg IV droperidol)†	+
Midazolam	Desaturation	90	Nil	—	0.46
Combination	Desaturation/airway obstruction	20	19	20 mg IV diazepam (immediate desaturation)	0.24
Combination	Hypotension	72	Nil	—	0.34

—, No additional sedation; *nil,* no sedation so the dose and time is not required; +, test was positive for alcohol, but no value.
*Time of adverse reaction or administration of additional sedation after the study drug was administered.
†Additional sedation administered after the adverse reaction.

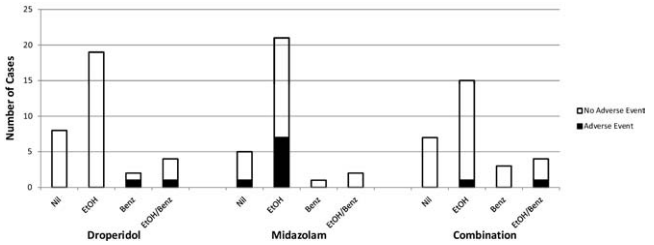

Figure 5. Column graphs of all 91 patients divided into their treatment arms and each of these divided again into 4 groups: EtOH, alcohol intoxication on admission; Benz, administration of a benzodiazepine for additional sedation in the first hour; Nil, neither alcohol intoxication nor additional benzodiazepine; and EtOH/Benz, both alcohol intoxication and administration of a benzodiazepine for additional sedation in the first hour. Each column represents the total number of patients in that group and the filled (black) column is the number who had drug-related adverse effects.

combination when used through the intramuscular route. In addition, although droperidol and the combination appeared to be similar, according to the primary outcomes and adverse effects, the Altered Mental Status Scale scores show that the combination resulted in much deeper sedation, with the potential for respiratory depression in the first 2 hours.

There are few controlled trials investigating the effectiveness and safety of droperidol for the sedation of agitated patients[12,13] and only 1 previous randomized controlled trial of intramuscular droperidol, to our knowledge.[2] All these previous studies demonstrated similar safety with droperidol and more sedative-type adverse drug effects with benzodiazepines. Extrapyramidal adverse effects, including dystonic reactions, did not occur in our study and have been reported in only 1% to 4% of patients in previous controlled trials,[2,12,13] more commonly with intravenous administration.[10,13] Hypotension has been reported in previous studies with both midazolam and droperidol,[10,13] and in our study hypotension occurred in 1 patient receiving midazolam and 1 receiving the combination (Table 3). Two of the previous studies, including the study of intramuscular sedation, found that further sedation was more commonly required after benzodiazepine administration.[2,12]

Intramuscular droperidol and midazolam resulted in a similar duration of violent and acute behavioral disturbance, but more additional sedation was required with midazolam. Midazolam caused more adverse effects because of oversedation, and there was no evidence of QT prolongation associated with droperidol. The study provides further evidence that midazolam, particularly through the intramuscular route, has unpredictable effects and a high rate of adverse reactions in this setting.

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Table E1. Altered mental status score used for the taken from Martel et al.[2]

Score	Responsiveness	Speech	Facial Expression	Eyes
4	Combative, violent, out of control	Loud outbursts	Agitated	Normal
3	Very anxious, agitated	Loud outbursts	Agitated	Normal
2	Anxious, agitated	Loud outbursts	Normal	Normal
1	Anxious, restless	Normal	Normal	Normal
0	Responds easily to name, speaks in normal tone	Normal	Normal	Clear, no ptosis
–1	Lethargic response to name	Mild slowing and thickening	Mild relaxation	Glazed or mild ptosis <1/2 eye
–2	Responds only if name is called loudly	Slurring or prominent slowing	Marked relaxation	Glazed and marked ptosis >1/2 eye
–3	Responds only after mild prodding	Few recognizable words	Marked relaxation, slacked jaw	Glazed and marked ptosis >1/2 eye
–4	Does not respond to mild prodding or shaking	Few recognizable words	Marked relaxation, slacked jaw	Glazed and marked ptosis >1/2 eye