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Preventing ICU Subsyndromal Delirium Conversion to Delirium with Low Dose IV Haloperidol: A Double-Blind, Placebo-Controlled Pilot Study

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Abstract

Objective—To compare the efficacy and safety of scheduled low-dose, haloperidol vs. placebo for the prevention of delirium [Intensive Care Delirium Screening Checklist (ICDSC) ≥ 4)] administered to critically ill adults with subsyndromal delirium (ICDSC = 1-3).

Design—Randomized, double-blind, placebo-controlled trial.

Setting—Three 10-bed ICUs (2 medical; 1 surgical) at an academic medical center in the U.S.

Patients—Sixty-eight mechanically ventilated patients with subsyndromal delirium without complicating neurologic conditions, cardiac surgery or requiring deep sedation.

Interventions—Patients were randomly assigned to receive intravenous haloperidol 1 mg or placebo every six hours until either delirium (ICDSC ≥ 4 with psychiatric confirmation), therapy ≥ 10 days or ICU discharge occurred.

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Measurements and Main Results—Baseline characteristics were similar between the haloperidol (n=34) and placebo (n=34) groups. A similar number of patients given haloperidol [12/34 (35%)] and placebo [8/34 (23%)] patients developed delirium (p=0.29). Haloperidol use reduced the hours per study day spent agitated (SAS ≥ 5) (p=0.008), but did not influence the proportion of 12-hour ICU shifts patients' spent alive without coma (SAS ≤ 2) or delirium (p=0.36), the time to first delirium occurrence (p=0.22) nor delirium duration (p=0.26). Days of mechanical ventilation (p=0.80), ICU mortality (p=0.55) and ICU patient disposition (p=0.22) were similar in the two groups. The proportion of patients who developed QTc-interval prolongation (p=0.16), extrapyramidal symptoms (p=0.31), excessive sedation (p=0.31) or new-onset hypotension (p=1.0) that resulted in study drug discontinuation was comparable between the two groups.

Conclusions—Low-dose scheduled haloperidol, initiated early in the ICU stay, does not prevent delirium and has little therapeutic advantage in mechanically ventilated, critically ill adults with subsyndromal delirium.

Keywords

delirium; haloperidol; prevention; Randomized Controlled Trial

Introduction

Delirium is commonly associated with critical illness (1, 2). In addition to the fear it elicits in patients, delirium is linked to a prolonged duration of mechanical ventilation and intensive care unit (ICU) stay and reduced post-ICU functionality and quality of life (1-3). Subsyndromal delirium is part of an outcome-predicting spectrum of delirium symptoms and is present when the Intensive Care Delirium Screening Checklist (ICDSC) score is 1 to 3 out of 8 (4, 5). A critically ill patient who develops subsyndromal delirium, compared to one who develops neither delirium (ICDSC ≥ 4) nor subsyndromal delirium, is more likely to die in the ICU, spend more time hospitalized and to be discharged to a long-term care facility rather than home (4).

Recent Society of Critical Care Medicine (SCCM) practice guidelines strongly advocate the use of non-pharmacologic strategies such as early mobilization and daily sedation interruption to prevent delirium in critically ill adults (6-8). However, a recommendation regarding the use of a pharmacologic delirium prevention strategy (e.g. dexmedetomidine, antipsychotic therapy) was not made since no published evidence clearly demonstrates the benefit of such an intervention in critically ill adults (6-9). Medications can easily be administered in the ICU and thus critical care clinicians are interested in the use of any pharmacologic intervention(s) that might provide added benefit to that which is observed with the use of non-pharmacologic delirium prevention interventions alone.

Perioperative use of low-dose antipsychotic therapy in non-critically ill patients undergoing elective major surgery, where a short post-operative ICU admission is sometimes required, has been shown to reduce delirium burden (i.e., delirium incidence, duration or both) (10-16). However the results of these investigations cannot be extrapolated to the critically

ill given the different mechanisms, risk factors and outcomes of delirium that exist between the ICU and non-ICU populations (9, 17, 18).

Antipsychotic administration in the ICU is controversial (9, 19-21) and has not been studied in critically ill patients with subsyndromal delirium. One single-center, uncontrolled, before-after analysis suggested that the administration of haloperidol throughout the period of critical illness may reduce delirium and lower mortality (19). However, the results from two randomized, placebo-controlled studies in critically ill adults, where nearly half the patients in each study were delirium-free at the time of randomization, suggests that administration of haloperidol throughout the ICU stay will not reduce days spent with delirium or coma or alter clinically meaningful outcomes such as delirium duration, time on mechanical ventilation or post-ICU disposition (20, 21). Since the role of haloperidol as a strategy to prevent delirium in critically ill adults remained unclear, we sought to test the hypothesis that the administration of IV haloperidol to mechanically ventilated, critically ill adults, patients with subsyndromal delirium would prevent conversion to delirium.

Methods

Setting

This randomized, double-blind, placebo-controlled trial was conducted, in three, 10-bed ICUs at Tufts Medical Center, a 320-bed academic medical center located in Boston, MA. Each of the three ICUs (2 medical, 1 surgical) were closed units and had the same well-established pain, sedation and delirium assessment practices. Pain was evaluated at least every 4 hours and treated when present. Level of sedation was evaluated at least every 4 hours using the Sedation Agitation Scale (SAS) and sedative therapy was titrated to maintain patients at a lightly sedated state (SAS=3). Choice of analgesic and sedative therapy was left to the discretion of the bedside clinician. All patients were managed with the same daily awakening-spontaneous breathing trial (DA-SBT) protocol (22). A delirium screening protocol, in place in all three units for more than a decade, that clinicians received regular educational updates regarding and that had been used in multiple controlled ICU studies, mandated the evaluation of all ICU patients for the presence of delirium by the bedside nurse each shift using the ICDSC (Supplemental appendix) (5, 23-25). If the patient is deeply sedated (SAS = 2) or in coma (SAS=1), the protocol advocates that no ICDSC assessment be performed (and the ICDSC is considered negative by default) until wakefulness is achieved with DA and the patient reaches a SAS of least 3 (5, 26).

Patients

At the time of ICU admission, and on a daily basis for up to 3 days, the daily sedation and cognitive status of consecutive mechanically ventilated patients admitted to any of the three study ICUs and expected by the ICU team to have an ICU admission ≥ 24 hours, was categorized by the investigative team (based on the SAS and ICDSC assessments documented by the bedside nurse over the prior 24 hour) as having: 1) persistent deep sedation or coma, 2) delirium, 3) subsyndromal delirium or 4) neither delirium nor subsyndromal delirium. The presence of delirium precluded further consideration of a patient for the study. If subsyndromal delirium was present, and an addition ICDSC

evaluation by a member of the investigative team confirmed its presence, the patient was considered eligible and screened for study exclusion criteria (Table 1). In general, patients were excluded from the study if they were deemed to be at greater risk for experiencing a haloperidol-associated safety concerns (e.g., age ≥ 85 years, severe dementia) or had a condition that might preclude delirium evaluation (e.g. ICU admission because of an acute neurologic injury). Given a concern that any beneficial effect of a pharmacologic delirium prevention intervention could wane over the course of the ICU stay, patients admitted in the ICU for 4 or more days were excluded from the study. The Tufts Medical Center institutional review board approved the study and written informed consent was obtained from each subject's legally authorized representative prior to study randomization.

Interventions

Subjects were randomized in blocks of four to receive either haloperidol (1mg IV every six hours) or placebo in a 1:1 ratio by means of a computer generated random number table with treatment allocation known only to the investigational pharmacist. Haloperidol was chosen over other antipsychotic agents given its benefit in reducing delirium incidence or burden in patients undergoing major surgery and the fact that it can be administered intravenously (11, 12, 14). Published data regarding the pharmacodynamic response of haloperidol in the critically ill does not exist. The daily dose of haloperidol used (4 mg) in the study was therefore based on the fact that this is a dose that has been used in other ICU clinical studies (19, 20) and in non-ICU, non-delirium investigations has been shown to reliably occupy 60% of dopamine-2 receptors (27). Each study dose was prepared by the investigational pharmacy so that an identical looking 0.5 mL tuberculin syringe contained 0.2 mL of either haloperidol 1mg or 5% dextrose in water (D5W). Subjects, clinicians and all study personnel were blinded to study drug assignment. Each dose of the study drug was administered by the bedside nurse as a slow IV push over 1 minute into a pre-existing IV line and then flushed with 10mL of D5W. Study medication was administered until one of the following occurred: delirium, ICU discharge, 10 days of therapy had elapsed or an adverse effect necessitating study drug discontinuation was described.

The use of dexmedetomidine and off-study antipsychotic therapy was not allowed unless medically necessary during the period of study drug administration. All decisions regarding sedation and analgesia therapy and ventilator management were left to the discretion of the ICU team. All patients were managed with the same DA-SBT protocol (22). An early mobilization protocol was implemented in one of the three study ICUs part-way through the study (8).

Study Outcomes and Endpoints

All subjects were evaluated for the presence of delirium using the ICDSC-based protocol described above. A study investigator confirmed the presence of delirium by the bedside nurse using the ICDSC assessment; any disagreement was resolved through consensus. The presence of delirium was subsequently confirmed by a consultation psychiatrist using Diagnostic and Statistical Manual of Mental Disorders (DSM-IV) criteria (27); discordance between the psychiatric consultation and the bedside nurse and study investigator's ICDSC assessments were resolved through consensus.

At the time of enrollment, the following baseline demographics were collected: age, gender, severity of illness as estimated by both the Acute Physiology and Chronic Health Evaluation II (APACHE-II) (28),and Sequential Organ Failure Assessment (SOFA) score (29), ICU type, number of days of ICU admission before study enrollment, location before both hospitalization and ICU admission, primary reason for ICU admission, the Informant Questionnaire on Cognitive Decline in the Elderly (IQCODE) score (30), a history of moderate alcohol use (≥ 2 drinks per day) or depression (as evidenced by antidepressant use at the time of admission), the Pre-Deliric Delirium Risk Score (31), the use of continuous IV sedation and opioid therapy and the baseline SAS and ICDSC scores. The SAS was used to evaluate level of sedation every 4 hours with a SAS score ≥ 5 representing agitation (26).

The QTc-interval was measured by the bedside nurse every 6 hours using the bedside monitor. If an observed episode of potential QTc-interval prolongation (≥ 500 msec or ≥ 60 msec above baseline) was confirmed by a 12-lead ECG then the patient was excluded from the study unless the patient was concomitantly receiving a non-study medication with the potential to prolong the QTc interval (32, 33). In this scenario, if the ICU team felt that this medication could be discontinued, the study medication was continued for a further 12 hours and only discontinued if the QTc-interval remained prolonged. Signs of extrapyramidal symptoms (EPS) were monitored twice daily. If EPS were felt to be present, the subject was examined by an attending neurologist, who in consultation with the ICU team, decided whether study removal was warranted. When the subject was deemed to be excessively sedated by the ICU team and receiving a sedating medication, the sedating medication was held (or decreased) until the subject reached the team's desired wakefulness goal. In situations where excessive sedation persisted after study drug administration, and the subject was not receiving another sedating medication, the subject was removed from the study. Blood pressure was monitored 30 minutes after each study dose. Subjects with persistent hypotension (SBP ≤ 90 mmHg) despite adequate fluid resuscitation in whom the ICU team felt that haloperidol was the primary causative factor were excluded from the study. All subject-initiated episodes of device removal were documented.

The primary study outcome was the incidence of delirium that developed during the period of study drug administration. Secondary delirium-related outcomes included the incidence of delirium that developed during ICU admission, the time to delirium occurrence, the proportion of 12 hour ICU shifts without delirium, and among those subjects who developed delirium, the duration of delirium until if first resolved for ≥ 12 hours. Other secondary efficacy outcomes included the hours per study day spent agitated, the proportion of 12 hour ICU shifts without coma and without either coma or delirium, and among study days a continuous sedative was administered, the proportion of days DA protocol criteria was met and DA was completed, subjects ever receiving early mobilization, use of dexmedetomidine or non-study antipsychotic therapy, days of mechanical ventilation, duration of both ICU and hospital stay, and both ICU and hospital death. The disposition of subjects after hospital discharge was categorized into one of four groups: home, rehabilitation facility, chronic care facility, and death.

Data Analysis

Given the absence of a published controlled study evaluating the efficacy of antipsychotic therapy for the prevention of delirium in critically ill adult at the time this study was designed, we relied on an unpublished retrospective analysis of 72 consecutive ICU patients from our institution who developed subsyndromal delirium. Among patients exposed to ≥ 24 hours of haloperidol therapy during the period of sub-syndromal delirium, 2 of 16 (13%) developed delirium whereas 24 of 56 (43%) of patients not exposed to haloperidol developed delirium. Accordingly, we estimated using a 2-sided alpha level of 0.05 that we would need to enroll 34 subjects in each group to achieve 80% power to find a difference in the progression to delirium of at least 10%. .

Data were analyzed using an intention-to-treat principle. Outcomes were compared using the Mann-Whitney *U* test (expressed as median and IQR) or the chi-square test. Fisher's exact tests were used for categorical data with rare events. For outcomes reported as a percentage of the time study drug was administered, a percentage was first calculated for each subject and then the median (IQR) was reported for each group. To further explore the timing of delirium onset, Cox regression analysis was used to model time to delirium onset and the hazard ratio of treatment with haloperidol vs. placebo was computed together with its 95% confidence interval. Should a subject die in the ICU without developing delirium, sensitivity analyses were done by assigning these cases 'worst case' outcomes and 'best case' outcomes and redoing each of the analyses to test each hypothesis to see if the study conclusions would change. A $p \leq .05$ was considered significant for all analyses. All statistical analyses were performed using Statistical Analysis Solutions (SAS) version 9.4 (SAS; Cary, NC).

Results

Among 1, 358 patients initially screened, 879 (64.7%) were excluded due to persistent deep sedation/coma [282 (20.8%)], delirium [282 (20.8%)] and neither subsyndromal delirium nor delirium [313 (23.1%)] (Figure 1). Among the 481 (35.4%) patients with subsyndromal delirium deemed eligible, 413 (85.9%) were excluded leaving 68 subjects to be randomized. No subjects withdrew from the study and thus 68 subjects were included in the final analysis. Baseline characteristics were not statistically different between the two study groups (Table 2). Subjects were primarily medical, were frequently admitted with sepsis or acute respiratory distress syndrome, were severely ill, often had multiple baseline risk factors for delirium, and were enrolled, on average, within 24 hours of being admitted to the ICU (17).

The early treatment of subsyndromal delirium with haloperidol (vs. placebo) did not prevent conversion to delirium during study drug administration [12/34 (35.3%) vs. 8/34 (23.5%); p = 0.29] (Table 2). For 18 of the 19 subjects who developed delirium, the bedside nurse, study investigator and study psychiatrist were in full agreement that delirium was present. For one subject in the haloperidol arm, shortly after the bedside nurse and study investigator each deemed delirium to be present, and before the psychiatrist could conduct his assessment, the patient experienced an acute hypoxic event and subsequently required deep sedation to manage mechanical ventilatory support. The patient subsequently died of a cardiac arrest 12 hours later that was not felt to be related to study participation.

Use of haloperidol (vs. placebo) also did not affect the proportion of subjects who developed delirium during the ICU admission (35.3 vs. 26.5%, p = 0.43) (Table 3). Among subjects who developed delirium, the time to the first occurrence of delirium (p=0.22) (Figure 2) and the median (IQR) days of delirium before it first resolved was similar between the haloperidol [2(2-3)] and placebo [3(2-4)] groups (p=0.26). Subjects having delirium on each study day are presented in Figure 3. Haloperidol-treated subjects spent less [median (IQR)] hours per day agitated [0 (0-2) vs. 2 (1-6); p=0.008]. However, use of haloperidol (vs. placebo) did not affect the median (IQR) proportion (%) of 12 hour nursing shifts that subjects' were coma-free [100 (87-100) vs. 100 (91-100); p=0.71] or both coma- and delirium-free [91 (67-100) vs. 94 (80-100); p=0.36]. Use of haloperidol did not influence days spent on mechanical ventilation (p=0.79) or in the ICU (p=0.66) nor either ICU (p=0.29) or hospital (p=0.40) disposition (Table 4).

The proportion of subjects' experiencing an unexpected (ie. non-protocolized) serious adverse event was similar [2.9 % (haloperidol) vs. 8.8%, p=0.3]. None of these serious adverse events were felt by the investigative team to be related to study drug administration. Only one study subject (in the placebo group) self-extubated and required re-intubation. The proportion of subjects where study medication was discontinued because of a protocolized haloperidol-associated safety concern was not different between the haloperidol and placebo (20.6% vs. 5.9, p=0.15) groups (Table 5).

Discussion

Our investigation, the first randomized, double-blind, placebo-controlled trial to evaluate the prophylactic use of low-dose haloperidol in mechanically ventilated, critically ill adults, suggests that the early initiation of scheduled, low-dose, haloperidol does not prevent delirium among patients with subsyndromal delirium and who are at high risk for developing delirium, and may in fact lead to greater delirium. Use of haloperidol failed to reduce the time to first delirium, duration of delirium or the hours spent with delirium during the ICU stay. While the number of hours patient's spent agitated in the ICU was reduced, the clinical significance of this result remains unknown given that haloperidol use was not associated with a change in the days that mechanical ventilation was required nor a change in either ICU or hospital disposition. Protocolized haloperidol-related safety concerns were four-times greater in the patients exposed to haloperidol although this outcome was not a primary endpoint of the study.

Although being a single-center pilot study, our investigation has many strengths. Clinicians, investigators, patients and their families remained blinded to treatment allocation. The use of randomization allowed the two patient groups to be well-matched. Medical, surgical and trauma patients were all enrolled, and with study screening starting on the first ICU admission day, randomization occurred an average of one day after ICU admission. The study center had extensive experience using the SAS and the ICDSC (5, 23-26). The use of a well-established DA-SBT protocol allowed each patient to be evaluated for delirium when maximally awake and a psychiatrist with extensive ICU experience confirmed the presence of all delirium (22). No study patient received off-study antipsychotic therapy during the

study and the method by which common haloperidol-related adverse effects were monitored and managed was protocolized a-priori.

The results of our investigation differ from controlled studies where the administration of low-dose antipsychotic therapy to surgical patients has been shown to reduce delirium prevalence, delay its occurrence and/or shorten its duration (10-16). While some of the patients in these investigations required short-term, post-operative ICU care (14-16), very few would be considered to be deemed to be critically ill. Risk factors for delirium that are different between elective surgery patients and the critically ill may help explain the lack of benefit we observed with the use of haloperidol (17, 18, 33). Critically ill patients may be at greater risk for experiencing haloperidol-associated adverse effects (20, 21, 34). Given the frequency of adverse effects necessitating haloperidol discontinuation that were observed and the fact that monitoring for adverse effects is less stringent in routine ICU practice, haloperidol use to prevent delirium in critically ill patients with subsyndromal delirium is difficult to justify. Until results from larger, prospective controlled studies either confirm or refute our findings, clinicians should follow recommendations from the recent SCCM pain, agitation and delirium guidelines and avoid using antipsychotics to prevent delirium (6). Instead, critical care clinicians should focus on delirium risk factor reduction and early patient mobilization (6-8, 35-38).

Limitations of our study must also be acknowledged. Our pilot investigation may have been too small to detect a difference in delirium with the use of haloperidol if one exists. The fact that the absolute difference in delirium incidence was almost 13% greater in the haloperidol group suggests that a benefit with haloperidol use, if one truly exists, is likely small or that the incidence of delirium is higher. The rigorous study criteria we chose, although common among studies evaluating pharmacologic delirium prevention and treatment strategies in the critically ill, led to only 14% of patients with subsyndromal delirium actually being enrolled and thus the external validity of our study may be limited (20, 21, 25). There may be patients excluded from our study (e.g., not requiring mechanical ventilation or older than 85 years) who might have benefited from haloperidol therapy.

The high proportion of patients receiving continuous IV sedation may have led to a greater proportion of patients being deemed to have subsyndromal delirium and thus potentially eligible for study enrollment. The use of strategies known to affect ICU delirium occurrence, although not protocolized for the purposes of the study, were similar between the two groups. While compliance with a well-established DA-SBT protocol was high, early mobilization was in place in only one of the three study ICU studies (7). Randomization, in this medical ICU, was similar between haloperidol (n=15) and placebo (n=16) groups. The results from our single-center study might be different from that which could be observed at a center with a different patient mix or delirium prevention practices. Dexmedetomidine, although not shown to prevent delirium in the critically ill and administered to fewer than 15% of subjects, may have affected the rate of delirium reported (39, 40). While patients were randomized an average of 24 hours after ICU admission, the initiation of haloperidol at the onset of critical illness may have led to a different result. Use of a higher dose of haloperidol may have also led to different results. Lastly, we cannot exclude that surgical

critically ill patients with subsyndromal delirium may not benefit from haloperidol given that they represented less than one-third of the total subjects (15).

The role for haloperidol and other antipsychotics to prevent delirium in critically ill adults needs to be studied in large studies that have power to measure differences in an outcome like mortality (41). Future investigations should also evaluate the role of treating subsyndromal delirium in the ICU with antipsychotic therapy on post-ICU outcomes such PTSD, depression, long-term cognition, sleep quality and functionality (42, 43). The agitation-sparing effect of haloperidol requires further investigation (21). In conclusion, this double-blind, randomized pilot study suggests that other than a reduction in agitation, the administration of low-dose IV haloperidol in critically ill adults with subsyndromal delirium may not prevent delirium occurrence and is associated with potential safety concerns.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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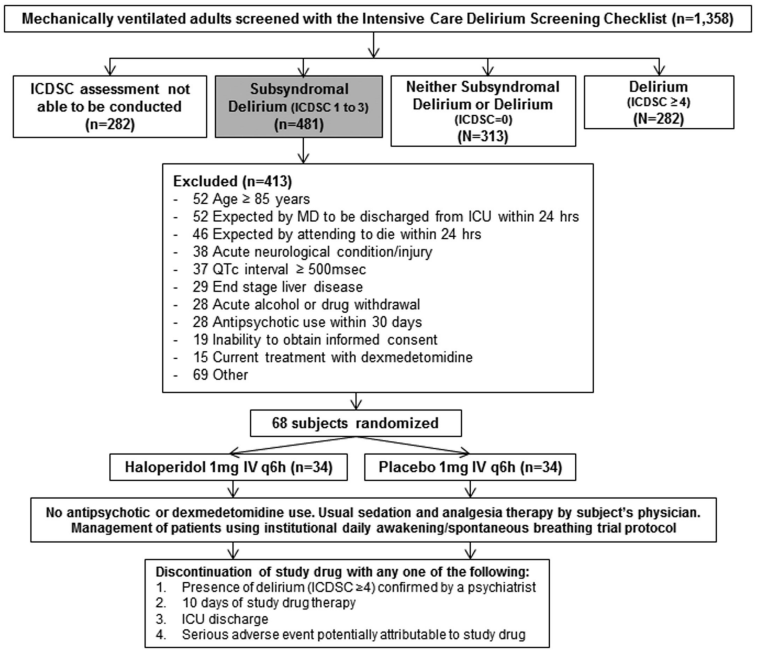

Figure 1.

Patient screening, enrollment, and randomization. ICDSC, Intensive Care Delirium Checklist

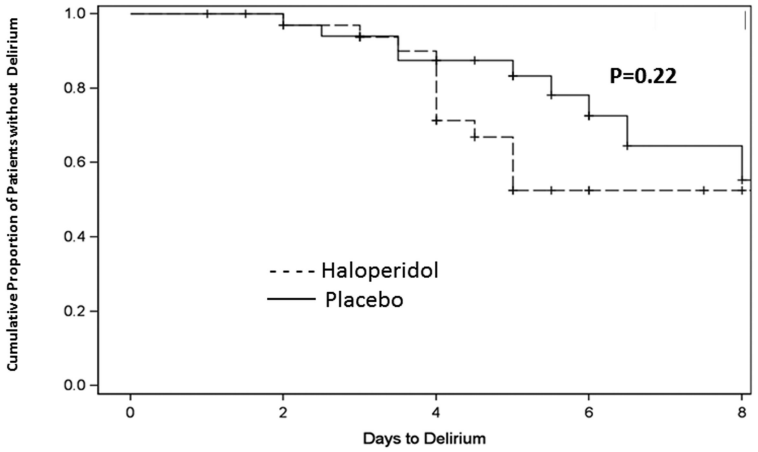

Figure 2.
Kaplan-Meier plot for time to first delirium occurrence between haloperidol and placebo groups

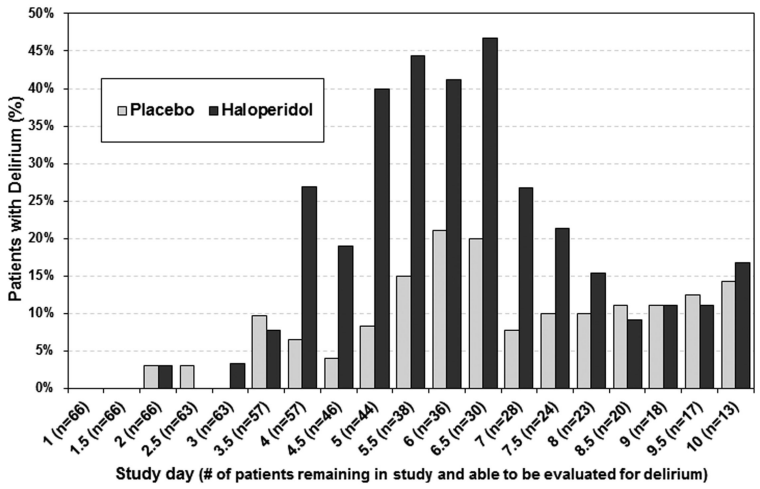

Figure 3.

Presence of delirium on each study day between the haloperidol and placebo groups.

Table 1

Study exclusion criteria

Age ≥ 85 years
History of severe dementia (documented history and/or IQCODE score ≥ 4) (30)
Acute neurological injury primary reason for ICU admission
History of schizophrenia or a formal thought disorder
Antipsychotic use in the prior 30 days
Current treatment with a neuromuscular blocker or dexmedetomidine
Persistent use of deep sedation (SAS score ≤ 2) where daily awakening unlikely (26)
Acute alcohol or drug withdrawal
History of end stage liver failure
QTc interval > 500 msec (32)
Current drug therapy with a class Ia, Ic or III antiarrhythmic (other than amiodarone)
History of haloperidol allergy
History of neuroleptic malignant syndrome
Recent cardiac surgery
Patients expected by attending physician to die within 24 hours
Patients expected by the attending physician to be discharged from the ICU within 24 hrs
Inability to obtain informed consent
Pregnancy

IQCODE: Informant Questionnaire on Cognitive Decline in the Elderly; ICDSC: Intensive Care Delirium Screening Checklist; SAS: Sedation-Agitation Scale

Table 2

Baseline characteristics

	Haloperidol (n=34)	Placebo (n=34)	P value
Age, yrs	61.7 ± 16.9	59.3 ± 14.9	0.53
Male, N (%)	18 (52.9)	20 (58.8)	0.63
APACHE II, at study enrollment	19 [17-23]	20 [17-24]	0.53
SOFA score, at study enrollment	4 [3- 6]	6 [3- 8]	0.10
ICU type, N (%)			
Medical	23 (67.6)	25 (73.5)	0.60
Surgical	11 (32.4)	9 (26.5)	0.43
Days in ICU before enrollment	1 [0-2]	1 [0-2]	0.32
Location before hospitalization, N (%)			0.19
Home with spouse	17 (50.0)	19 (55.9)	
Home alone	9 (26.5)	5 (14.7)	
Home with other family member(s)	5 (14.7)	6 (17.6)	
Rehabilitation facility	3 (8.8)	2 (5.9)	
Assisted living facility/nursing home	0	1 (2.9)	
Other	0	1 (2.9)	
Location before ICU admission, N (%)			0.35
Emergency department	13 (38.2)	14 (41.2)	
Hospital ward	10 (29.4)	6 (17.6)	
ICU at an outside hospital	5 (14.7)	4 (11.8)	
Ward at an outside hospital	3 (8.8)	7 (20.6)	
Other	3 (8.8)	3 (8.8)	
Admission diagnosis, N (%)			0.31
Sepsis/ARDS	15 (44.1)	18 (52.8)	
Respiratory failure	7 (20.6)	4 (11.8)	
Gastrointestinal	3 (8.8)	4 (11.8)	
Trauma	3 (8.8)	2 (5.9)	
Cardiac	3 (8.8)	1 (2.9)	
Non-traumatic major surgery	2 (5.9)	2 (5.9)	
Other	1 (2.9)	3 (8.8)	
IQCODE score (30)	3 [3-3]	3 [3-3]	0.82
Moderate alcohol use, N (%)	14 (41.1)	16 (47.1)	0.62
Depression, N (%)	6 (17.6)	5 (14.7)	0.74
Pre-Deliric score (%) (31)	51 [36-75]	48 [38-71]	0.54
Continuous IV sedation at randomization, N (%)			0.77
Midazolam	5 (14.7)	5 (14.7)	
Propofol	25 (73.5)	26 (76.4)	
None	3.0 (8.8)	1.9 (2.9)	
Continuous IV opioid at randomization, N (%)	14 (41.2)	19 (55.9)	0.33
SAS at study entry (26)	3 [3-3]	3 [3-3]	0.85

	Haloperidol (n=34)	Placebo (n=34)	P value
ICDSC score at study entry (5)	2 [1-2]	2 [2-2]	

Reported as N (%), mean ± SD or median [interquartile range]

APACHE = acute physiologic and chronic health evaluation

ARDS = acute respiratory distress syndrome

ICDSC = intensive care delirium screening checklist

ICU = intensive care unit

IV = intravenous

IQCODE = informant questionnaire on cognitive decline in the elderly.

SAS = sedation agitation scale

SOFA = sequential organ failure assessment

Table 3

Clinical outcomes during study drug administration

	Haloperidol (n=34)	Placebo (n=34)	P value
Delirium [% (n)]	35.3 (12)	23.5 (8)	0.287
Duration of first episode of delirium (d)	2 [1-2]	3 [2-4]	0.261
Proportion of 12 hour ICU nursing shifts without coma or delirium (%)	91 [67-100]	94 [80-100]	0.359
Proportion of 12 hour ICU nursing shifts without delirium (%)	100 [75-100]	100 [92-100]	0.236
Proportion of 12 hour ICU nursing shifts without coma (%)	100 [87-100]	100 [91-100]	0.708
Hours per study day spent agitated [SAS ≥ 5] (%)	0 [0-2]	2 [1-6]	0.008
Days where a continuous IV sedative administered (%)	95 [41-100]	82 [60-100]	0.666
Days where DA criteria met and DA completed (%)	100 [88-100]	100 [76-100]	0.667
Days where SBT criteria met and SBT completed (%)	100 [100-100]	100 [100-100]	0.499
Patients ever receiving early mobilization (%)	11.8 (4)	20.6 (7)	0.476
Dexmedetomidine exposure after randomization [% (n)]	14.7 (5)	11.8	0.731
Exposure to non-study antipsychotic therapy [% (n)]	0 (0)	0 (0)	1.000
Duration of first episode of subsyndromal delirium (d)	3 [2-4]	3 [2-5]	0.323

Reported as % (n) or median [interquartile range]

ICU, intensive care unit; IV, intravenous; DA, daily awakening; SBT, spontaneous breathing trial.

Table 4

Other clinical outcomes

	Haloperidol (n=34)	Placebo (n=34)	P value
Days of mechanical ventilation	4.5 [3-7]	5 [3-8]	0.79
Duration of ICU stay (d)	6.5 [4-8]	7 [4-9]	0.66
ICU disposition (%)			0.22
Died in ICU	26.5	20.6	
Hospital ward	70.6	58.8	
Rehabilitation	2.9	14.7	
Hospital disposition (%)			0.40
Died in hospital	26.5	20.6	
Home	41.2	26.5	
Rehabilitation	29.4	47.1	
Long term care facility	2.9	2.9	

ICU, intensive care unit.

Table 5

Patients where study medication was stopped due to a protocolized haloperidol-associated event.

	Haloperidol (n=34)	Placebo (n=34)	P value
QTc interval prolongation [% (n)]	11.8 (4)	2.9 (1)	0.16
Extrapyramidal symptoms [% (n)]	2.9 (1)	0	0.31
Excessive sedation (% (n)]	2.9 (1)	0	0.31
Hypotension [% (n)]	2.9 (1)	2.9 (1)	1.00