ORIGINAL ARTICLE

Haloperidol for the Treatment of Delirium in ICU Patients

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ABSTRACT

BACKGROUND

Haloperidol is frequently used to treat delirium in patients in the intensive care unit (ICU), but evidence of its effect is limited.

METHODS

In this multicenter, blinded, placebo-controlled trial, we randomly assigned adult patients with delirium who had been admitted to the ICU for an acute condition to receive intravenous haloperidol (2.5 mg 3 times daily plus 2.5 mg as needed up to a total maximum daily dose of 20 mg) or placebo. Haloperidol or placebo was administered in the ICU for as long as delirium continued and as needed for recurrences. The primary outcome was the number of days alive and out of the hospital at 90 days after randomization.

RESULTS

A total of 1000 patients underwent randomization; 510 were assigned to the haloperidol group and 490 to the placebo group. Among these patients, 987 (98.7%) were included in the final analyses (501 in the haloperidol group and 486 in the placebo group). Primary outcome data were available for 963 patients (97.6%). At 90 days, the mean number of days alive and out of the hospital was 35.8 (95% confidence interval [CI], 32.9 to 38.6) in the haloperidol group and 32.9 (95% CI, 29.9 to 35.8) in the placebo group, with an adjusted mean difference of 2.9 days (95% CI, –1.2 to 7.0) (P=0.22). Mortality at 90 days was 36.3% in the haloperidol group and 43.3% in the placebo group (adjusted absolute difference, –6.9 percentage points [95% CI, –13.0 to –0.6]). Serious adverse reactions occurred in 11 patients in the haloperidol group and in 9 patients in the placebo group.

CONCLUSIONS

Among patients in the ICU with delirium, treatment with haloperidol did not lead to a significantly greater number of days alive and out of the hospital at 90 days than placebo. (Funded by Innovation Fund Denmark and others; AID-ICU ClinicalTrials.gov number, NCT03392376; EudraCT number, 2017-003829-15.)

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*A full list of the investigators in the AID-ICU trial group is provided in the Supplementary Appendix, available at NEJM.org.

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Delirium is defined as an acute disturbance in attention and awareness and is the most common sign of acute brain dysfunction among critically ill patients.[1,2] The condition is estimated to affect 30 to 50% of patients being treated in the intensive care unit (ICU) and is associated with increased morbidity and mortality.[3-7]

Haloperidol, a typical antipsychotic compound, continues to be the most frequently used agent to treat delirium in ICU patients. Results of an international inception-cohort study that were published in 2018 showed that approximately half the ICU patients with delirium received haloperidol.[8] The use of haloperidol is not supported by clinical practice guidelines because evidence of its effect is limited.[1] A recent systematic review[9] of trials comparing haloperidol with other pharmacologic interventions for the treatment of delirium in ICU patients identified only one placebo-controlled trial and concluded that the evidence for the use of haloperidol to treat delirium in ICU patients was sparse and inconclusive. We conducted the Agents Intervening against Delirium in the Intensive Care Unit (AID-ICU) trial to investigate whether treatment with haloperidol would lead to a greater number of days alive and out of the hospital than placebo; other clinically important outcomes in ICU patients with delirium were also evaluated.

Methods

Trial Design and Oversight

This was a multicenter, blinded, parallel-group, placebo-controlled clinical trial with centralized randomization. Patient screening was performed between June 14, 2018, and April 9, 2022, at 18 general ICUs in Denmark, Finland, the United Kingdom, Italy, and Spain, and patients at 16 of these ICUs underwent randomization (Tables S1 and S2 in the Supplementary Appendix, available with the full text of this article at NEJM.org). Oral and written informed consent was obtained for each patient according to national regulations. The enrollment of patients was predominantly allowed as an emergency procedure because all the patients lacked the capacity to provide consent owing to delirium. Consent or assent was obtained from a physician independent of the trial (who represented the patient as a legal guardian) before enrollment of the patient, after which oral and written informed consent to continue participation was obtained from a relative or an authorized representative of the patient and later from the patient after the capacity to provide informed consent had returned. If consent was withdrawn, the assigned haloperidol or placebo was discontinued, and permission was sought to continue collection of trial data for analysis in accordance with national regulations.

The management committee (the members of which are listed in the Supplementary Appendix) designed the trial protocol, which was approved by the relevant ethics committees, medical authorities, and data-protection agencies in participating countries. The trial protocol[10] and statistical analysis plan[11] have been published previously (before enrollment of the last patient) and are available at NEJM.org.

The conduct of the trial, patient safety, and completeness and accuracy of the data were ensured by an external monitoring committee according to the Good Clinical Practice directive of the European Union and were also overseen centrally by staff from the coordinating center. An independent data and safety monitoring committee assessed safety in an interim analysis, which was performed when 500 patients had been followed for 90 days. The members of the management committee wrote the manuscript and made the decision to submit it for publication. The authors vouch for the accuracy and completeness of the data and for the fidelity of the trial to the protocol. The funding organizations had no influence on the design or conduct of the trial or on the collection, analysis, or reporting of the data and do not have any ownership of the data.

Trial Population

Patients 18 years of age or older who had been admitted to an ICU for an acute condition and had received a positive result on a screening test for delirium according to either the Confusion Assessment Method for the ICU (CAM-ICU)[12] or the Intensive Care Delirium Screening Checklist (ICDSC) were assessed for eligibility.[13] Patients were screened for delirium in the ICU at least twice daily by clinical staff using the tool that was standard at their site (either the CAM-ICU or ICDSC). Delirium was considered to be present if a patient had a positive CAM-ICU assessment or if four or more symptoms of delirium were present on the ICDSC assessment. We encouraged in-

vestigators and clinicians at the trial sites to screen all the patients fulfilling the inclusion criteria for enrollment in the trial. Patients could be assessed for eligibility throughout the entire ICU stay.

RANDOMIZATION AND BLINDING

Eligible patients were randomly assigned in a 1:1 ratio to receive haloperidol or placebo (isotonic saline). Randomization was performed at a central location with the use of a computer-generated assignment sequence with randomly varying block sizes and was stratified according to trial site and delirium motor subtype (hyperactive or hypoactive). Clinicians, patients, investigators, outcome assessors, statisticians, and members of the data and safety monitoring committee were unaware of the trial-group assignments. Haloperidol and placebo were contained in identical ampules with identical labeling. The solutions were colorless and indistinguishable from each other (Fig. S1).

TRIAL INTERVENTIONS

Enrolled patients were assigned to receive either intravenous haloperidol at a dose of 2.5 mg (0.5 ml of 5-mg-per-milliliter haloperidol solution) or 0.5 ml of placebo (isotonic saline) three times daily. At the discretion of the clinicians, additional as-needed doses could be administrated up to a maximum total daily dose of 20 mg of haloperidol (4 ml of 5-mg-per-milliliter haloperidol solution) or 4 ml of placebo. In cases of uncontrollable delirium, patients could receive rescue medication (propofol, benzodiazepines, or α_2-agonists) at the discretion of the clinical team. During the intervention period, patients were screened for delirium twice daily by clinical staff using either the CAM-ICU or ICDSC. Administration of haloperidol or placebo was paused when the patient did not have delirium, as determined by two consecutive negative CAM-ICU assessments or ICDSC scores on the same day (scores on the ICDSC range from 0 to 8, with a score of <4 indicating negative and ≥4 positive delirium status). If the patient had another episode of delirium, administration of the haloperidol or placebo was resumed. The intervention period was from randomization until discharge or death in the ICU, up to a maximum of 90 days after randomization; if a patient was readmitted to the ICU within the 90-day trial period and had delirium, the assigned haloperidol or placebo was resumed. The use of other antipsychotic drugs during ICU stay was not allowed; all other interventions were performed at the discretion of the clinicians.

OUTCOME MEASURES

The primary outcome was the number of days alive and out of the hospital within 90 days after randomization. The two components of this composite outcome, death and length of hospital stay at 90 days, were also assessed. Secondary outcomes were the number of days alive without delirium or coma (as defined according to the Richmond Agitation–Sedation Scale, the Ramsay Sedation Scale, the Motor Activity Assessment Scale, or the Glasgow Coma Scale; the scores used to define coma according to these instruments are provided in the Supplementary Appendix) in the ICU at 90 days, the number of days alive without mechanical ventilation at 90 days, the number of patients with one or more serious adverse reactions to haloperidol in the ICU, the total number of serious adverse reactions to haloperidol in the ICU, the number of patients receiving rescue medication, and the number of days with rescue medication per patient. We calculated the predicted 90-day mortality among the patients using the Simplified Mortality Score for Intensive Care Unit (SMS-ICU), on which scores range from 0 to 42, with higher scores predicting higher 90-day mortality.[14] Data were obtained from the patients' medical records and hospital registries by the trial investigators or their delegates. Additional details about outcomes are provided in the Supplementary Appendix.

STATISTICAL ANALYSIS

Data from the AID-ICU cohort study[8] provided us with the likely distribution of days alive and out of the hospital at 90 days in the placebo group. Assuming that haloperidol would lead to a 15% lower incidence of death in the hospital and a shorter hospital admission time than placebo, such that the combined effect would reflect an 8% greater mean number of days alive and out of the hospital, we estimated that 1000 patients would be required for the trial to have 90% power to detect such a difference at an alpha level of 5%.

Analyses of the primary and secondary outcomes were performed in the intention-to-treat population, which included all patients who had

undergone randomization, received the assigned haloperidol or placebo,[15] and provided consent for their data to be used. The per-protocol population included the patients in the intention-to-treat population, with the exclusion of those who had one or more major protocol violation. Additional information on the definitions and occurrence of major protocol violations is provided in the Supplementary Appendix.

The statistical analyses were performed according to the published statistical analysis plan by the first and tenth authors, who were unaware of the trial-group assignments.[11] All analyses were adjusted for stratification variables (trial site and delirium motor subtype). In the primary analysis, we used a linear-regression model to estimate the adjusted mean difference between the groups. Because of the nonnormal distribution, we bootstrapped 95% confidence intervals; 50,000 resampling iterations were used in the bootstrap. The Kryger Jensen and Lange[16] test was used to estimate the P value because this test was designed for distributions of outcome results that show many patients with a value of zero, which would be the case for the number of days alive and out of the hospital, the outcome used in the current trial. The two components of the primary outcome — mortality and hospital length of stay at 90 days — were analyzed with the use of binary logistic regression and a linear-regression model, respectively.

The secondary analysis of the primary outcome was adjusted for additional predefined risk factors at baseline (the presence of traumatic brain injury, stroke, mental illness, neurodegenerative illness, alcohol overconsumption, substance abuse, benzodiazepine use, tobacco smoking, predicted 90-day mortality, and use of haloperidol before ICU admission). The primary outcome was further analyzed in the per-protocol population, and heterogeneity of treatment effect was evaluated in prespecified subgroups that were defined at baseline according to trial site, delirium motor subtype (hyperactive vs. hypoactive), ICU admission type (medical vs. surgical), sex (female vs. male), age (<69 years vs. ≥69 years[8]), patients with one or more risk factors of delirium (yes vs. no), and disease severity (SMS-ICU score <25 vs. ≥25). With regard to the secondary outcomes, days alive without delirium or coma in the ICU and days alive without mechanical ventilation were analyzed with the use of a linear-regression model; the number of patients with one or more serious adverse reactions and the number of patients receiving rescue medication were analyzed with the use of logistic regression; and the total number of serious adverse reactions and the number of days with use of rescue medication per patient were analyzed with the use of Poisson regression.

A two-sided P value of less than 0.05 was considered to indicate statistical significance in the analysis of the primary outcome. If the between-group difference with respect to the primary outcome was found to be significant, a hierarchical testing procedure would be applied, in which the alpha level (5%) would be divided evenly among the six secondary outcomes, corresponding with a significance level of 0.83%. To account for correlation among outcomes, the 0.83% alpha level was rounded to 1%, and consequently, 99% confidence intervals were used. If the between-group difference with respect to the primary outcome was not found to be significant, the secondary outcomes would be considered to be explorative in accordance with the principles in Jakobsen et al.[17,18]

No imputation for missing data was performed because the number of patients with missing data was low for all outcomes and was therefore considered to be negligible.[19] We performed all statistical analyses with R software, version 4.1.2 (R Core Team, R Foundation for Statistical Computing). Additional details regarding the statistical methods are provided in the Supplementary Appendix.

RESULTS

TRIAL POPULATION

We enrolled 1000 patients; 510 were randomly assigned to the haloperidol group, and 490 to the placebo group. A total of 13 patients (9 in the haloperidol group and 4 in the placebo group) were excluded after randomization (Fig. 1). We obtained data on the primary outcome from 963 patients (96.3%) and data on 90-day mortality and the secondary outcomes from 987 patients (98.7%). At the time of randomization, 447 patients had hyperactive delirium and 540 patients had hypoactive delirium. Patient characteristics at baseline were reasonably balanced between the trial groups (Table 1 and Table S3 in the Supplementary Appendix). The trial patients

were representative of patients in the participating ICUs.

INTERVENTION AND ADHERENCE TO PROTOCOL

During the 90-day intervention period, the patients in the haloperidol group received a median daily dose of 8.3 mg (1.7 ml) of haloperidol for a median of 3.6 days, and the patients in the placebo group received a median daily dose equivalent to 9.0 mg (1.8 ml) of haloperidol for 3.3 days (Table 2). The two groups received a similar cumulative dose of haloperidol or placebo, and the amount of haloperidol or placebo that was administered as needed was similar in the two groups (Table 2). Open-label antipsychotic agents were administered to 66 patients (13.2%) in the haloperidol group and 63 patients (13.0%) in the placebo group, primarily because they had with-

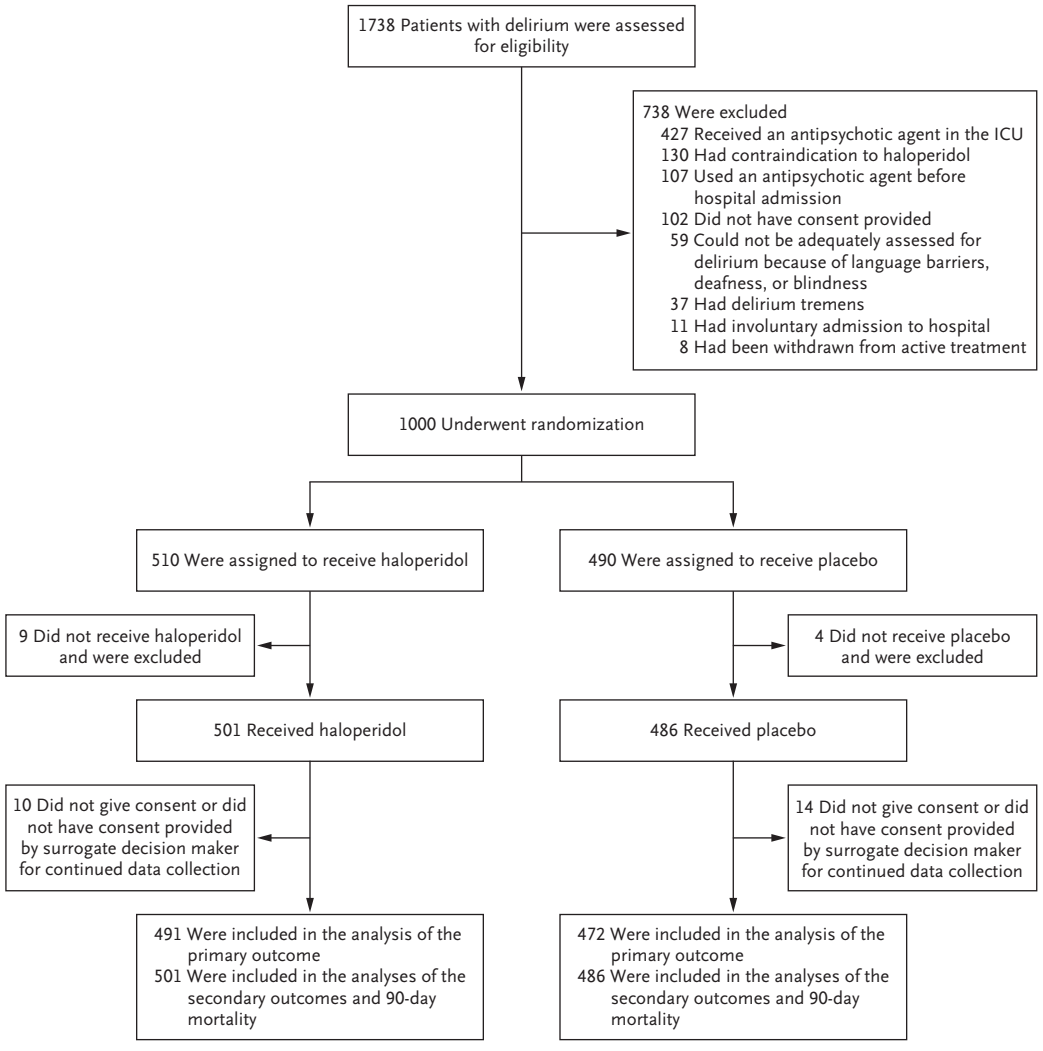


Figure 1. Screening, Randomization, and Follow-up of Patients.

Adults with delirium who had been admitted to an intensive care unit (ICU) for an acute condition underwent screening. Patients could have more than one reason for exclusion; a total of 129 patients met two or more exclusion criteria. A total of 13 patients were withdrawn after randomization because they did not receive the assigned haloperidol or placebo (7 had consent withdrawn by a surrogate decision maker before receipt of the first dose of haloperidol or placebo, 4 did not meet inclusion criteria, and 2 were discharged from the ICU before receipt of the first dose of haloperidol or placebo). Data on the primary outcome were missing for 24 patients, but data on vital status at 90 days were available for all patients, with the exception of 1 in the placebo group.

Table 1. Demographic and Clinical Characteristics of the Patients at Baseline.*

Characteristic	Haloperidol (N=501)	Placebo (N=486)
Median age (IQR) — yr	70 (62–76)	71 (63–76)
Female sex — no. (%)	177 (35.3)	161 (33.1)
Risk factors for delirium — no. (%)		
Traumatic brain injury within 6 mo	8 (1.6)	7 (1.4)
Stroke within 6 mo	12 (2.4)	17 (3.5)
History of mental illness	29 (5.8)	29 (6.0)
History of neurodegenerative disease	2 (0.4)	3 (0.6)
Active tobacco smoker	156 (31.2)	147 (30.2)
Alcohol overconsumption	85 (17.0)	77 (15.8)
Other substance abuse	9 (1.8)	9 (1.9)
Received benzodiazepines before hospitalization	13 (2.6)	17 (3.6)
Received benzodiazepines in hospital before randomization	166 (33.1)	143 (29.4)
Received haloperidol in hospital before ICU admission	34 (6.8)	33 (6.8)
Coexisting condition — no. (%)†		
Hematologic cancer	33 (6.6)	31 (6.4)
Metastatic cancer	15 (3.0)	15 (3.1)
Covid-19	37 (7.4)	52 (10.7)
Admission type — no. (%)		
Surgical	183 (36.5)	153 (31.5)
Medical	318 (63.5)	333 (68.5)
Use of organ support at randomization — no. (%)		
Mechanical ventilation‡	320 (63.9)	305 (62.8)
Vasopressors or inotropes§	272 (54.3)	239 (49.2)
Renal-replacement therapy¶	77 (15.4)	70 (14.4)
Predicted 90-day mortality — SMS-ICU score‖	34.7±15.4	34.6±15.4
Delirium motor subtype at randomization — no. (%)		
Hypoactive	277 (55.3)	263 (54.1)
Hyperactive	224 (44.7)	223 (45.9)
Delirium screening tool used — no. (%)		
CAM-ICU	385 (76.8)	382 (78.6)
ICDSC	116 (23.2)	104 (21.4)
Median time from hospital admission to ICU admission (IQR) — days	1.0 (0.0–5.0)	1.0 (0.0–5.0)
Median time from ICU admission to randomization (IQR) — days	3.9 (1.8–9.7)	4.1 (1.6–8.9)

* Plus–minus values are means ±SD. Data on baseline characteristics were available for all 987 patients in the intention-to-treat population. CAM-ICU denotes Confusion Assessment Method for the Intensive Care Unit, ICDSC Intensive Care Delirium Screening Checklist, ICU intensive care unit, and IQR interquartile range.

† Information on coexisting conditions was collected only for the prediction score (i.e., the Simplified Mortality Score for the Intensive Care Unit [SMS-ICU]); beginning on March 11, 2020, information on the presence of coronavirus disease 2019 (Covid-19) was also collected.

‡ Mechanical ventilation was defined as invasive or noninvasive mechanical ventilation, including use of a continuous positive airway pressure (CPAP) mask or CPAP by means of tracheostomy within 24 hours before randomization. Intermittent CPAP was not defined as mechanical ventilation.

§ Use of vasopressors or inotropes was defined as continuous infusion of norepinephrine, epinephrine, phenylephrine, vasopressin analogues, dopamine, dobutamine, milrinone, or levosimendan within the 24 hours before randomization.

¶ Renal-replacement therapy was defined as short-term or prolonged intermittent or continuous renal-replacement therapy within the 24 hours before randomization.

‖ The predicted 90-day mortality was calculated with the use of the SMS-ICU,[14] on which scores range from 0 to 42 (corresponding with a range of predicted 90-day mortality of 3.3 to 91.0%). Additional details regarding the SMS-ICU score are provided in the Supplementary Appendix.

Table 2. Use of Haloperidol or Placebo, Rescue Medication, Open-Label Antipsychotic Agents, or Restraint in the ICU after Randomization.

Variable	Haloperidol (N = 501)	Placebo (N = 486)
Median duration of trial intervention (IQR) — days	3.6 (1.8–6.8)	3.3 (1.8–6.2)
Median no. of daily doses received (IQR)†	3.4 (2.8–4.5)	3.6 (3.0–5.1)
Median total no. of doses received (IQR)	13.0 (7.0–26.0)	13.0 (7.0–26.0)
Median daily dose (IQR) — mg/day*	8.3 (6.8–11.4)	9.0 (7.4–12.5)
Median cumulative dose (IQR) — mg	32.5 (17.5–62.5)	32.5 (17.5–62.5)
Received one or more as-needed doses — no. (%)	364 (72.7)	358 (73.7)
Median total no. of as-needed doses received (IQR)	5.0 (2.0–10.0)	5.0 (3.0–12.0)
Use of rescue medication		
Propofol†		
No. of patients (%)	88 (17.6)	73 (15.0)
Median duration of use (IQR) — days	2.0 (1.0–4.3)	3.0 (1.0–4.0)
α_2-agonist†		
No. of patients (%)	239 (47.7)	253 (52.1)
Median duration of use (IQR) — days	3.0 (2.0–5.0)	3.0 (2.0–5.0)
Benzodiazepines†		
No. of patients (%)	137 (27.3)	158 (32.5)
Median duration of use (IQR) — days	2.0 (1.0–4.0)	2.0 (1.0–4.0)
Use of open-label antipsychotic agents		
No. of patients (%)	66 (13.2)	63 (13.0)
Median duration of use (IQR) — days	3.7 (1.0–10.3)	3.0 (1.3–8.8)
Use of restraint during delirium — no. (%)	9 (1.8)	10 (2.1)

* The median number of daily doses received (the number of doses per day) and the median daily dose (in milligrams per day) were calculated as the cumulative number of doses received and the cumulative dose received, respectively, divided by the total number of days that the patient received haloperidol or placebo.

† Rescue medication was defined as the use of propofol, α_2-agonists, or benzodiazepines to treat uncontrollable delirium (e.g., agitation and insomnia). Patients could receive more than one rescue medication on the same day.

drawn consent. The duration of the use of open-label antipsychotic agents was similar in the two groups (Table 2).

OUTCOMES

At 90 days, the mean number of days alive and out of the hospital was 35.8 (95% confidence interval [CI], 32.9 to 38.6) in the haloperidol group and 32.9 (95% CI, 29.9 to 35.8) in the placebo group (adjusted mean difference, 2.9; 95% CI, –1.2 to 7.0; P=0.22) (Table 3 and Fig. S2). Similar results were found in the sensitivity analysis in which the primary outcome was further adjusted for risk factors at baseline and in the per-protocol analysis (Tables S4 and S5). No heterogeneity of treatment effect was found for the primary outcome in the prespecified subgroups (Fig. 2).

At 90 days, 182 of the 501 patients (36.3%) in the haloperidol group and 210 of the 486 patients (43.3%) in the placebo group had died (adjusted absolute difference, –6.9 percentage points; 95% CI, –13.0 to –0.6) (Fig. 2 and Table 3). The adjusted mean difference in the length of hospital stay between the haloperidol group and placebo group was 2.3 days (95% CI, –0.6 to 5.1) (Table 3). Similar results were observed in the per-protocol analysis (Table S4). The adjusted mean difference between the haloperidol group and the placebo group in the number of days alive without delirium or coma was 5.1 (99% CI, –1.2 to 11.3) and in the number of days alive without

Table 3. Primary and Secondary Outcomes.*

Outcome	Haloperidol	Placebo	Adjusted Absolute Difference (95% or 99% CI)†	Adjusted Relative Risk (95% or 99% CI)†	P Value
Primary outcome					
Days alive and out of hospital at 90 days — raw mean no. (95% CI)‡	35.8 (32.9 to 38.6)	32.9 (29.9 to 35.8)	2.9 (–1.2 to 7.0)§	NC	0.22¶
Death — no./total no. (%)‖	182/501 (36.3)	210/485 (43.3)	–6.9 (–13.0 to –0.6)**	0.84 (0.72 to 0.98)	
Length of hospital stay — raw mean no. of days (95% CI)††	28.8 (26.7 to 30.8)	26.4 (24.4 to 28.5)	2.3 (–0.6 to 5.1)§	NC	
Secondary outcomes					
Days alive without delirium or coma — raw mean no. (99% CI)‡‡	57.7 (53.4 to 62.0)	52.6 (48.0 to 57.1)	5.1 (–1.2 to 11.3)§	NC	
Days alive without mechanical ventilation — raw mean no. (99% CI)	57.9 (53.7 to 62.2)	53.9 (49.5 to 58.3)	4.0 (–2.2 to 10.1)§	NC	
Serious adverse reaction in ICU — no./total no. (%)	11/501 (2.2)	9/486 (1.9)	0.4 (–1.9 to 2.7)**	1.20 (0.33 to 5.45)	
Use of rescue medication — no./total no. (%)§§	288/501 (57.5)	302/486 (62.1)	–4.0 (–11.8 to 3.6)**	0.93 (0.82 to 1.06)	
Days with use of rescue medication per patient — raw mean no. (99% CI)	2.9 (2.3 to 3.5)	2.9 (2.3 to 3.4)	0.1 (–0.7 to 0.9)	NC	

* NC denotes not calculated; the adjusted relative risk was not calculated because the calculation was not specified in the statistical analysis plan.
† The adjusted absolute difference and the adjusted relative risk are presented with 95% confidence intervals in the analyses of the primary outcome and with 99% confidence intervals in the analyses of the secondary outcomes.
‡ Data regarding the primary outcome were missing for 24 patients (10 in the haloperidol group and 14 in the placebo group). The 95% confidence intervals for the means were calculated with the use of the standard formula: mean ± z value × (standard deviation/square root of the sample size).
§ Adjusted absolute difference and bootstrapped confidence intervals were obtained with a linear-regression model adjusted for stratification variables.
¶ The P value was obtained with the use of the Kryger Jensen and Lange test. The linear-regression model with adjustment for stratification variables yielded a P value of 0.16.
‖ Death was assessed at 90 days; data were missing for 1 patient in the placebo group.
** Data were missing for 24 patients.
†† The adjusted absolute difference is given in percentage points.
‡‡ Days alive without delirium or coma were assessed at 90 days; the presence of coma or delirium was assessed only in the ICU.
§§ Rescue medication for uncontrollable delirium was used according to the protocol and included propofol, α_2-agonists, and benzodiazepines.

mechanical ventilation was 4.0 (99% CI, –2.2 to 10.1) (Table 3 and Figs. S3 and S4).

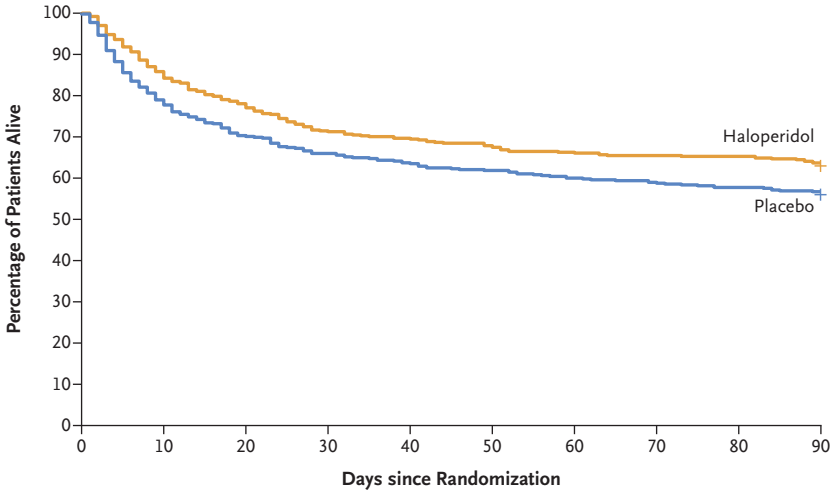
SAFETY

The number of patients with one or more serious adverse reactions was similar in the two groups (Table 3 and Table S6). No patient had more than one serious adverse reaction. The number of patients receiving rescue medication and the number of days with use of rescue medication were similar in the two groups (Tables 2 and 3 and Fig. S5). The assigned trial regimen was discontinued in 12 patients (2.4%) in the haloperidol group and 7 patients (1.4%) in the placebo group because of QTc prolongation (Table S7). Another 15 patients (3.0%) in the haloperidol group and 24 patients (4.9%) in the placebo group had their assigned trial regimen discontinued by clinical staff for other reasons. Physical restraint was used in 9 patients (1.9%) in the haloperidol group and 10 patients (2.1%) in the placebo group (Table 2).

DISCUSSION

In this multicenter, blinded, randomized, placebo-controlled trial involving adult patients with delirium in the ICU, we found that the number of days alive and out of the hospital at 90 days did not differ significantly between the haloperidol group and placebo group. Our findings add to those of the Modifying the Impact of ICU-Associated Neurological Dysfunction–USA (MIND-USA)

A Overall Survival



No. at Risk										
Haloperidol	501	430	391	358	349	340	332	328	327	319
Placebo	485	383	341	320	309	300	291	286	280	275

B Main and Subgroup Analyses of the Primary Outcome

Subgroup	No. of Patients		Mean No. of Days Alive and Out of Hospital (95% CI)		Adjusted Mean Difference (95% or 99% CI)
	Haloperidol	Placebo	Haloperidol	Placebo	
All patients	501	486	35.8 (32.9 to 38.7)	32.9 (29.9 to 35.8)	2.9 (–1.2 to 7.0)
Motor subtype of delirium					
Hyperactive	217	216	39.3 (34.9 to 43.7)	34.9 (30.4 to 39.3)	4.4 (–4.0 to 12.7)
Hypoactive	274	256	33.0 (29.3 to 36.8)	31.2 (27.3 to 35.1)	1.6 (–5.5 to 8.7)
Age					
<69 yr	221	189	39.3 (35.2 to 43.4)	39.1 (34.5 to 43.8)	0.4 (–7.9 to 8.8)
≥69 yr	270	283	32.9 (29.0 to 36.9)	28.7 (24.9 to 32.4)	3.8 (–3.4 to 11.0)
Sex					
Male	319	314	35.6 (32.1 to 39.1)	32.4 (28.8 to 36.0)	3.4 (–3.3 to 10.0)
Female	172	158	36.2 (31.2 to 41.2)	33.8 (28.6 to 39.1)	2.0 (–7.3 to 11.2)
Admission type					
Surgical	178	149	36.9 (32.4 to 41.5)	36.9 (31.9 to 42.0)	–1.1 (–10.0 to 7.8)
Medical	313	323	35.2 (31.5 to 38.8)	31.0 (27.4 to 34.6)	4.5 (–2.3 to 11.3)
Risk factors for delirium					
Yes	308	279	37.5 (33.9 to 41.1)	33.0 (29.2 to 36.8)	4.5 (–2.2 to 11.3)
No	183	193	32.9 (28.2 to 37.6)	32.7 (27.9 to 37.4)	0.9 (–8.0 to 9.9)
SMS-ICU					
<25	383	361	38.5 (35.3 to 41.7)	35.3 (32.0 to 38.6)	2.9 (–3.2 to 9.1)
≥25	108	111	26.3 (20.3 to 32.3)	25.1 (19.0 to 31.1)	1.2 (–10.0 to 12.5)

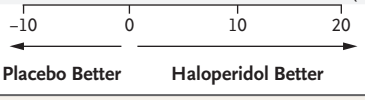


Figure 2. Overall Survival and Subgroup Analyses of the Primary Outcome.

Panel A shows the survival curves for the haloperidol group and placebo group in the intention-to-treat population. Data were censored at day 90. For one patient in the placebo group, we could not obtain vital status at 90 days; this patient was not included in the plot. Panel B shows the main and subgroup analyses of the number of days alive and out of the hospital within 90 days after randomization (primary outcome). The sizes of the boxes in the plot corresponds to the number of patients in each subgroup. In the main analysis that included all patients, the adjusted mean difference between the haloperidol group and the placebo group is given with a 95% confidence interval. In the subgroup analyses, the adjusted mean differences are given with 99% confidence intervals. The results are shown for six of the seven predefined subgroups; the predefined subgroup of trial site was not included in the plot, but no heterogeneity of treatment effect was found. Heterogeneity of treatment effect was assessed with the use of a linear-regression model adjusted for stratification variables. Scores on the Simplified Mortality Score for Intensive Care Unit (SMS-ICU) range from 0 to 42, with higher scores predicting higher 90-day mortality; a score of 25 corresponds to a predicted risk of death at 90 days of 50.1%. Additional information on the subgroup definitions is provided in the Supplementary Appendix.

trial,[20] in which ICU patients with delirium were randomly assigned to receive haloperidol (192 patients), placebo (184 patients), or ziprasidone (190 patients). In that trial, no significant difference in the number of days alive without delirium or coma or in mortality at 90 days was observed between the haloperidol group and placebo group. As in our trial, few adverse events were observed in the haloperidol group. Although our results suggest that mortality may have been lower with haloperidol than with placebo, no conclusions may be drawn. Potential reasons for the suggestion of a between-group difference in mortality that was observed in our trial, as opposed to the findings of the MIND-USA trial, may include a larger sample size, broader inclusion criteria, older patient age, less use of open-label antipsychotic agents, and more patients with hyperactive delirium in our trial than in the MIND-USA trial.

The strengths of our trial include the blinded, placebo-controlled design; the large sample size; and the high level of completeness of data. The protocol and statistical analysis plan were published before the last patient underwent randomization. We used validated diagnostic tools for the assessment of delirium and enrolled a broad population of patients with hypoactive or hyperactive delirium who had been screened by clinicians, methods that may increase the generalizability of the results. The trial design allowed as-needed administration of haloperidol or placebo and the use of rescue medications so that clinical staff could safely care for patients with delirium while maintaining routine practices at their site.

The trial has several limitations. The low number of patients from international sites may limit the generalizability of the findings. The screening for delirium and eligibility that was performed by clinical staff probably resulted in some eligible patients being missed for inclusion and a lower enrollment of patients with hypoactive delirium than with hyperactive delirium. However, this screening process may have resembled clinical practice and ensured that patients could be enrolled after hours. The data on coexisting conditions beyond risk factors for delirium were sparse. The composite nature of the primary outcome may challenge the interpretation of the results, since the point estimate for mortality was lower and the point estimate for length of hospital stay was higher in the haloperidol group than in the placebo group. We did not collect detailed data on other sedatives, pain medications, or nonpharmacologic interventions administered to patients. Some patients were withdrawn from the trial (primarily owing to withdrawal of consent), which resulted in exposure to open-label antipsychotic agents in 13% of the trial population. However, the frequency of such withdrawal was similar in the two trial groups.

In the current trial involving ICU patients with delirium, the use of haloperidol did not lead to a significantly greater number of days alive and out of the hospital at 90 days than placebo.

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APPENDIX

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