Association Between Incident Delirium Treatment With Haloperidol and Mortality in Critically Ill Adults*

Matthew S. Duprey, PharmD, PhD[1]

John W. Devlin, PharmD, MCCM[1]

Johannes G. van der Hoeven, MD, PhD[2]

Peter Pickkers, MD, PhD[2]

Becky A. Briesacher, PhD[1]

Jane S. Saczynski, PhD[1]

John L. Griffith, PhD[3]

Mark van den Boogaard, RN, PhD[2]

OBJECTIVES: Haloperidol is commonly administered in the ICU to reduce the burden of delirium and its related symptoms despite no clear evidence showing haloperidol helps to resolve delirium or improve survival. We evaluated the association between haloperidol, when used to treat incident ICU delirium and its symptoms, and mortality.

DESIGN: Post hoc cohort analysis of a randomized, double-blind, placebo-controlled, delirium prevention trial.

SETTING: Fourteen Dutch ICUs between July 2013 and December 2016.

PATIENTS: One-thousand four-hundred ninety-five critically ill adults free from delirium at ICU admission having an expected ICU stay greater than or equal to 2 days.

INTERVENTIONS: Patients received preventive haloperidol or placebo for up to 28 days until delirium occurrence, death, or ICU discharge. If delirium occurred, treatment with open-label IV haloperidol 2 mg tid (up to 5 mg tid per delirium symptoms) was administered at clinician discretion.

MEASUREMENTS AND MAIN RESULTS: Patients were evaluated tid for delirium and coma for 28 days. Time-varying Cox hazards models were constructed for 28-day and 90-day mortality, controlling for study-arm, delirium and coma days, age, Acute Physiology and Chronic Health Evaluation-II score, sepsis, mechanical ventilation, and ICU length of stay. Among the 1,495 patients, 542 (36%) developed delirium within 28 days (median [interquartile range] with delirium 4 d [2–7 d]). A total of 477 of 542 (88%) received treatment haloperidol (2.1 mg [1.0–3.8 mg] daily) for 6 days (3–11 d). Each milligram of treatment haloperidol administered daily was associated with decreased mortality at 28 days (hazard ratio, 0.93; 95% CI, 0.91–0.95) and 90 days (hazard ratio, 0.97; 95% CI, 0.96–0.98). Treatment haloperidol administered later in the ICU course was less protective of death. Results were stable by prevention study-arm, predelirium haloperidol exposure, and haloperidol treatment protocol adherence.

CONCLUSIONS: Treatment of incident delirium and its symptoms with haloperidol may be associated with a dose-dependent improvement in survival. Future randomized trials need to confirm these results.

KEY WORDS: coma; delirium; haloperidol; intensive care; mortality; risk factors

Delirium, the phenotypic expression of acute encephalopathy (1), occurs in up to 50% of critically ill adults and is associated with a substantial burden to patients and their families, a longer length of ICU stay, and long-term cognitive impairment (2–6). These concerns, coupled with the

***See also p. 1363.**

DOI: 10.1097/CCM.0000000000004976

importance of treating certain delirium symptoms acutely (e.g., agitation, delusions), result in the frequent administration of antipsychotic medications like haloperidol to treat delirium in the ICU (7, 8). The use of haloperidol to treat ICU delirium persists despite three randomized trials (one pilot [9], one evaluating patients both with and without delirium [10], and one evaluating patients with delirium admitted with acute respiratory failure or shock [11], clearly demonstrating no benefit with haloperidol use on days spent with delirium and mortality). A recent practice guideline recommends haloperidol should not be routinely administered for ICU delirium treatment (12). Although haloperidol may help reduce agitation in critically ill adults with delirium (10), the presence of agitation is not associated with increased mortality (13).

Incident delirium refers to delirium occurring after (and not before) ICU admission; prevalent delirium refers to delirium occurring before or at ICU admission. Cohort studies have found an association between prevalent delirium and longer term mortality, although this association is highly dependent on ICU severity of illness (14). Recent data suggest incident delirium does not affect 28- or 90-day mortality (15). Prior ICU haloperidol delirium treatment randomized trials have enrolled patients with both prevalent and incident delirium (10, 11). Data suggest delays in treating delirium in the ICU are associated with increased mortality (16). A delay to the initiation of haloperidol after delirium occurrence may be greater with prevalent delirium than incident delirium particularly when delirium first occurs prior to ICU admission. The Prophylactic Haloperidol Use for Delirium in ICU Patients at High Risk for Delirium (REDUCE) trial, a multicenter, randomized, placebo-controlled ICU study of critically ill adults without delirium at the time of ICU admission, failed to demonstrate any benefit of administering low-dose haloperidol to prevent delirium (17). In the trial, when the prevention intervention failed and incident delirium occurred, clinicians immediately administered scheduled treatment haloperidol and titrated upwards using a symptom-driven approach.

The relationship between haloperidol used to treat incident delirium and its symptoms in the ICU and mortality remains unclear. We therefore performed a post hoc analysis of the REDUCE trial to evaluate the association between treatment haloperidol exposure and mortality in a population of critically ill adults without delirium at the time of ICU admission.

MATERIALS AND METHODS

Study Design and Population

This is a post hoc analysis of a three-armed, randomized, placebo-controlled trial evaluating haloperidol for the prevention of delirium in the ICU. The study design and results have been previously described (17, 18). In short, 1,789 critically ill adults from 21 Dutch ICUs with an expected ICU stay greater than or equal to 2 days, and who had neither delirium nor an acute neurologic injury at ICU admission, were randomized within 24 hours of ICU admission to receive haloperidol 2 mg IV q8h, haloperidol 1 mg IV q8h, or placebo for up to 28 days or until delirium, ICU discharge, or death occurred. Only the 1,495 patients (83.6%) with complete delirium and coma assessment data on all ICU days were included, regardless of haloperidol treatment exposure, and merged into one cohort for the current analysis (17). Patients were managed with a multimodal, nonpharmacologic delirium-reduction protocol focused on wakefulness, mobility, and sleep improvement. The REDUCE study was approved by the Arnhem-Nijmegen medical ethics committee (CMO-number 2012/424).

Exposures and Outcomes

Patients were assessed tid for up to 28 days from the time of ICU admission for the presence of coma (Richmond Agitation Sedation Scale [RASS] score ≤ –4) and delirium (Confusion Assessment Method for the ICU [CAM-ICU]) (19, 20). Delirium was deemed to be present on any day if greater than or equal to one CAM-ICU assessment was positive. If coma was present on a nondelirium day, this day was classified as a coma day. All other days were classified as days with neither delirium nor coma. Mortality was evaluated for 28 days and 90 days after enrollment. Baseline information including age, severity of illness (Acute Physiology and Chronic Health Evaluation [APACHE] II) score (21), presence of sepsis, requirement for mechanical ventilation, and ICU length of stay were also collected.

In patients where delirium occurred, the ICU clinical team was encouraged to immediately initiate open-label haloperidol starting at a dose of 2 mg tid. Using a delirium symptom-based approach, the clinical team was instructed to increase the treatment haloperidol dose up to a maximum dose of 5 mg tid. After 3 days of treatment, if delirium (and its symptoms) resolved, clinicians were instructed to halve the daily haloperidol dose. On the next

day, if delirium and its symptoms did not reoccur, the haloperidol dose was halved again and then stopped on the third delirium-free day. If delirium recurred during this dose-reduction phase, then haloperidol was resumed at the most recent effective dose. Nonstudy haloperidol use was not permitted in patients who did not develop delirium. The use of other antipsychotics (e.g., quetiapine) was not permitted. Analgesics and sedatives were administered at the discretion of the clinical ICU team. All data used in the analyses for this study were collected in accordance with the REDUCE study protocol (18).

Statistical Analysis

A time-varying Cox regression model was created for both 28- and 90-day mortality. Patients were followed from ICU admission to death; patients who survived to the mortality endpoint were censored. Each model controlled for several a priori-determined potential confounders: days spent with delirium and/or coma in the 28 days after ICU admission, patient age, baseline severity of illness, presence of sepsis during the ICU, the need for mechanical ventilation, and the competing risk of ICU length of stay. Treatment haloperidol was modeled as a continuous predictor using average daily treatment dose with hazard ratios (HRs) reported for each 1 mg increase. An interaction between time and treatment haloperidol administration was introduced to examine the potential time-varying nature of treatment haloperidol exposure. Additionally, we created a second model using a segmented time-dependent covariate accounting for ICU day and the dose of haloperidol administered on that day. A sensitivity analysis controlling for the random study treatment allocation to prevention haloperidol (i.e., haloperidol 2 mg IV tid, haloperidol 1 mg IV tid, or placebo) was conducted to study the impact of prevention study group assignment on the treatment haloperidol-mortality association of interest. Additional models were constructed to evaluate the association between total ICU haloperidol exposure (i.e., both prevention and treatment) and mortality. A per-protocol sensitivity analysis was conducted that excluded delirium-positive patients not exposed to treatment dose haloperidol, patients without delirium exposed to nonstudy haloperidol, or patients exposed to an antipsychotic other than haloperidol after incident delirium occurrence. We also stratified the model by delirium status to understand the role of open-label haloperidol in patients with and without delirium and controlled for days spent mechanically ventilated as an estimation of whether daily changes in severity in illness influenced our results (22, 23). The role of admission type (medical vs surgical) on the haloperidol-mortality association was evaluated, and we conducted an analysis controlling for clustering by study center. To ensure our model was not conditional on an indication for treatment, we created a post hoc model controlling for delirium and coma status as a segmented time-varying covariate. We also created a model not controlling for delirium or coma status. All data were analyzed using SPSS Version 24 (SPSS, Chicago, IL). A p value of less than 0.05 was considered statistically significant.

RESULTS

Among the 1,495 patients, 542 (36%) developed delirium for 4 days (2–7 d) (median [interquartile range]) within the first 28 days of ICU admission (duration 4 d [2–9 d]), and 489 (32%) received treatment haloperidol (**Table 1**). Patients, on average, were 66.3 years old, 61.8% male, and had a mean admission APACHE-II score of 19.2 ± 7.0. More than three quarters required mechanical ventilation, and close to one third were diagnosed with sepsis. Patients had similar characteristics regardless of delirium presence, receipt of treatment haloperidol (Table 1), or survival to 28 days (vs 90 d) (**Supplemental Table 1**, Supplemental Digital Content 1, http://links.lww.com/CCM/G236). Among the 542 delirium-positive patients, 11.9% never received open-label haloperidol, and among the 953 delirium-negative patients, 1.3% received open-label haloperidol; these subgroups were similar (**Supplemental Table 2**, Supplemental Digital Content 2, http://links.lww.com/CCM/G237). Among the 922 coma-positive patients, 45.1% received open-label haloperidol, and among the 573 coma-negative patients, 12.7% received open-label haloperidol; the coma-positive subgroup who received haloperidol had higher APACHE-II score, more sepsis, and longer ICU stays (**Supplemental Table 3**, Supplemental Digital Content 3, http://links.lww.com/CCM/G238).

Among the 922 patients spending greater than or equal to 1 day with coma in the 28 days after ICU admission, 2 days (1–5 d) were spent with coma. The greatest number of patients with delirium (211; 14.1%) occurred on ICU day 4 (**Supplemental Fig. 1**, Supplemental Digital Content 4, http://links.lww.com/CCM/G239). Among the 489 patients (32.7%) receiving ICU treatment haloperidol,

TABLE 1.
Demographics and Characteristics of Patients by Survival Status at 28 and 90 Days

Variable	Total, *n* = 1,495	Delirium Positive		Administration of Treatment Haloperidol	
		Yes, *n* = 542	No, *n* = 953	Yes, *n* = 489	No, *n* = 1,006
Age, mean ± SD, yr	66.3 ± 12.6	67.7 ± 11.4	65.5 ± 13.2	67.7 ± 11.4	65.6 ± 13.2
Male gender, *n* (%)	924 (61.8)	357 (65.9)	567 (59.5)	326 (66.7)	598 (59.4)
Acute Physiology and Chronic Health Evaluation-II score, mean ± SD[a]	19.2 ± 7.0	20.5 ± 6.8	18.5 ± 7.0	20.4 ± 6.8	18.7 ± 7.0
Sepsis, *n* (%)	467 (31.2)	203 (37.5)	264 (27.7)	184 (37.6)	283 (28.1)
Mechanical ventilation, *n* (%)	1156 (77.3)	508 (93.7)	648 (68.0)	459 (93.9)	697 (69.3)
ICU length of stay, median (IQR), d	4 (2–9)	9 (5–17)	3 (2–5)	9 (5–18)	3 (2–6)
Prediction of Delirium in ICU Patients score, mean ± SD[b]	25.8 ± 12.0	29.4 ± 11.5	23.8 ± 11.8	29.1 ± 11.3	24.2 ± 12.0
Delirium positive, *n* (%)	542 (36.3)	100 (100)	0 (0)	477 (97.5)	65 (6.5)
Days of delirium (in 28 d), median (IQR)	4 (2–7)	4 (2–7)	0 (0–0)	4 (2–8)	1 (1–2)
Coma positive, *n* (%)	922 (61.7)	461 (85.1)	461 (48.4)	416 (85.1)	506 (50.3)
Days of coma (in 28 d), median (IQR)	2 (1–5)	4 (2–7)	2 (1–3)	4 (2–7)	2 (1–3)
Days with either delirium or coma (in 28 d), median (IQR)	2 (0–5)	7 (4–12)	0 (0–2)	7 (4–12)	1 (0–2)
Reintubation, *n* (%)	143 (9.6)	101 (18.6)	42 (4.4)	95 (19.4)	48 (4.8)
ICU readmission, *n* (%)	151 (10.1)	70 (12.9)	81 (8.5)	59 (12.1)	92 (9.1)

IQR = interquartile range.

[a]Acute Physiology and Chronic Health Evaluation-II score ranges from 0 to 71; the higher the score, the more severely ill the patient and the higher the hospital mortality risk.

[b]Prediction of Delirium in ICU Patients score ranges from 0 to 100, representing the percentage risk that delirium occur during the complete ICU length of stay.

the average daily dose was 2.1 mg (1.0–3.8 mg) and never exceeded 4.5 mg. Treatment haloperidol was administered for 6 days (3–11 d) and continued after ICU discharge in only 10 patients (2.0%). The average daily dose of treatment haloperidol was greater for survivors (vs nonsurvivors) on all, but 5 of the 28 ICU days patients were administered haloperidol. A total of 10 delirium patients (0.7%) received olanzapine, and 29 (1.9%) received quetiapine.

Over 28 days of follow-up, each milligram of treatment haloperidol administered daily to a patient with delirium was associated with a 7% decrease in mortality (HR, 0.93; 95% CI, 0.91–0.95) (**Table 2**). This haloperidol dose-mortality reduction relationship was found to be time dependent. The association between haloperidol treatment and 28-day mortality decreased daily as haloperidol was administered later in the ICU course (HR, 1.003; 95% CI, 1.002–1.004) and was detected through ICU day 19 (**Fig. 1**). The association between open-label treatment haloperidol and reduced mortality was also observed when a segmented time-varying covariate structure for dose was used, although the association with the time-varying dose covariate was not significant (**Supplemental Table 4**, Supplemental Digital Content 5, http://links.lww.com/CCM/G240). Treatment haloperidol continued to be associated with a dose-dependent, time-dependent

TABLE 2.
Hazard Ratios for Risk of Death from Adjusted Time-Varying Cox Regression Models

Variable	28 d Mortality Hazard Ratio (95% CI)	90 d Mortality Hazard Ratio (95% CI)
Treatment haloperidol average daily dose (mg)	0.93 (0.91–0.95)	0.97 (0.96–0.98)
Interaction of time and haloperidol dose	1.003 (1.002–1.004)	1.0005 (1.0003–1.0007)
Total number of days with delirium or coma	1.13 (1.09–1.17)	1.07 (1.04–1.10)
Age	1.04 (1.03–1.06)	1.04 (1.03–1.05)
Acute Physiology and Chronic Health Evaluation-II score[a]	1.07 (1.05–1.09)	1.06 (1.05–1.08)
Sepsis	1.84 (1.42–2.39)	1.77 (1.40–2.23)
Mechanical ventilation	2.51 (1.68–3.75)	1.95 (1.38–2.75)
ICU length of stay	0.93 (0.90–0.95)	0.97 (0.99–0.99)

[a]APACHE-II score ranges from 0 to 71; the higher the score, the more severely ill the patient and the higher the hospital mortality risk.

reduction in mortality at 28 days when we considered study treatment arm allocation (HR, 0.93; 95% CI, 0.91–0.95) (**Supplemental Table 5**, Supplemental Digital Content 6, http://links.lww.com/CCM/G241), total haloperidol exposure (i.e., both prevention + treatment) (HR, 0.97; 95% CI, 0.96–0.98) (**Supplemental Table 6**, Supplemental Digital Content 7, http://links.lww.com/CCM/G242), and only those patients who had delirium and received treatment haloperidol (HR, 0.93; 95% CI, 0.91–0.95) (**Supplemental Table 7**, Supplemental Digital Content 8, http://links.lww.com/CCM/G243).

Over 90 days of follow-up, each milligram of treatment haloperidol administered was associated with a 3% decrease in mortality (HR, 0.97; 95% CI, 0.96–0.98), a weaker association with reduced mortality than observed at 28 days. This association with reduced mortality at 90 days also decreased as haloperidol was administered later in the course of the ICU admission (HR, 1.0005; 95% CI, 1.0003–1.0007). The association between open-label treatment haloperidol and reduced mortality at 90 days was also observed when a segmented time-varying covariate structure for dose was used, although the association with the time-varying dose covariate was not significant (Supplemental Table 4, Supplemental Digital Content 5, http://links.lww.com/CCM/G240). Treatment haloperidol continued to be associated with a dose-dependent, time-dependent reduction in mortality at 90 days when we considered study treatment arm allocation (HR, 0.97; 95% CI, 0.96–0.98) (**Supplemental Table 8**, Supplemental Digital Content 9, http://links.lww.com/CCM/G244), total haloperidol exposure (i.e., prevention + treatment) (HR, 0.98; 95% CI, 0.98–0.99)(**Supplemental Table 9**, Supplemental Digital Content 10, http://links.lww.com/CCM/G245), and only those patients who had delirium and received treatment haloperidol (HR, 0.97; 95% CI, 0.96–0.98) (**Supplemental Table 10**, Supplemental Digital Content 11, http://links.lww.com/CCM/G246).

Although open-label haloperidol administered to patients without delirium was not associated with a difference in either 28- and 90-day survival (**Supplemental Table 11**, Supplemental Digital Content 12, http://links.lww.com/CCM/G247), treatment haloperidol administered to delirium-positive patients continued to be associated with lower 28- and 90-day mortality (**Supplemental Table 12**, Supplemental Digital Content 13, http://links.lww.com/CCM/G248). When the daily requirement for mechanical ventilation, a potential marker for greater daily severity of illness, was controlled for, treatment haloperidol continued to be associated with a dose-dependent, time-dependent reduction at both 28 days (HR, 0.93; 95% CI, 0.91–0.95) and 90 days (HR, 0.97; 0.96–0.98) (**Supplemental Table 13**, Supplemental Digital Content 14, http://links.lww.com/CCM/G249). Controlling for surgical (vs medical) admission did not influence the reported association between daily treatment haloperidol and either 28- or 90-day mortality (**Supplemental Table 14**, Supplemental Digital Content 15, http://links.lww.com/CCM/G250).

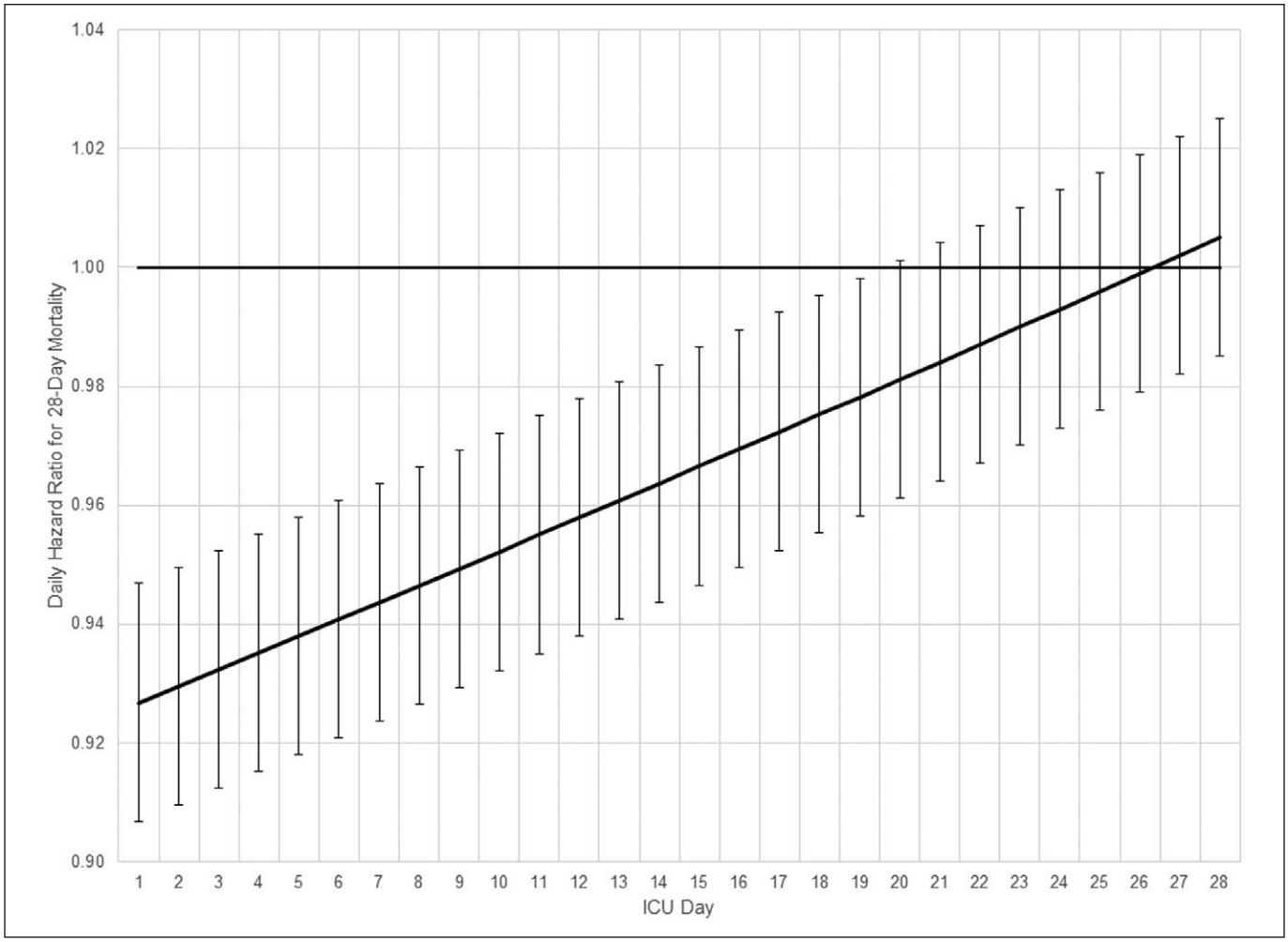

Figure 1. Time-varying hazard ratio for 28 d mortality for each additional milligram of haloperidol administered daily.

Controlling for clustering by study center had no relevant effect on the haloperidol-mortality association reported (**Supplemental Table 15**, Supplemental Digital Content 16, http://links.lww.com/CCM/G251). A sensitivity analysis accounting for the time-varying nature of delirium and coma did not change the direction of the association between haloperidol and mortality (**Supplemental Table 16**, Supplemental Digital Content 17, http://links.lww.com/CCM/G252). Last, removal of delirium or coma days from the model resulted in no change to the nature of the association between haloperidol and mortality (**Supplemental Table 17**, Supplemental Digital Content 18, http://links.lww.com/CCM/G253).

DISCUSSION

The REDUCE trial showed administration of haloperidol to a broad range of critically ill adults without delirium neither prevented delirium nor reduced mortality (17). This post hoc analysis of the REDUCE study cohort demonstrates that use of haloperidol to treat incident delirium, and where the haloperidol dose is titrated to resolve both delirium and its symptoms, may be associated with lower 28-day mortality in a dose-dependent, time-dependent manner. Sensitivity analysis reveals this survival benefit is demonstrated only in delirium-positive patients. Although an association between haloperidol and reduced mortality was still observed up to 90 days, it was lower than that observed at 28 days suggesting this effect may wane over time. Similar to sepsis, mortality at 90 days among patients with delirium may also be better attributed to the comorbidity burden of patients at baseline rather than the specific delirium care a patient receives during their ICU and post-ICU hospital stay (24, 25). Randomized studies are needed to confirm the results we report in both incident and prevalent delirium patients. Until this research is completed, ICU

clinicians should not assume treating delirium and its symptoms with haloperidol will reduce mortality.

Our analysis evaluated varying treatment doses of haloperidol and explored the interaction between haloperidol use and its administration time. By doing so, we found that when haloperidol is administered to patients where incident delirium occurs later in their ICU stay, any potential survival benefit decreases. Although patients with incident delirium were undoubtedly prescribed haloperidol to treat agitation, the presence of agitation itself does not influence any potential relationship between delirium occurrence and mortality (13). Although the results of our cohort analysis should be considered hypothesis generating and do not allow conclusions about causality to be made (26, 27), the administration of haloperidol occurred prior to death, and the protective effect of haloperidol on mortality we observed is dose dependent. Due to a lack of inflammatory biomarker data or delirium symptom data, we are not able to hypothesize on other potential mechanisms for the mortality benefit we observed, some which may be independent of the days spent with delirium or coma (28).

The conclusions we make from our cohort analysis run contrary to the results of two recent randomized controlled trials, the Modifying the Impact of ICU-Associated Neurologic Dysfunction-USA (MIND-USA) study (11) and the Haloperidol Effectiveness in ICU delirium (HOPE-ICU) trial (10). Unlike the patients in REDUCE, some of the patients in MIND-USA and HOPE-ICU had prevalent delirium. Among patients where delirium first occurred prior to ICU admission, a delay between first delirium onset and haloperidol initiation may have occurred. In HOPE-ICU, some of the patients did not have delirium at the time of randomization. It remains unclear how differences between the ICU adults enrolled in the HOPE-ICU (all mechanically ventilated medical or surgical) or the MIND-USA (acute respiratory failure or shock) trials and those enrolled in the REDUCE trial (medical or surgical with anticipated ≥ to 2 d ICU stay; approximately two thirds mechanically ventilated) influence the results we report.

Our analysis has potential limitations. Cohort studies like ours are more susceptible to selection bias than randomized trials like MIND-USA or HOPE-ICU. The daily rate by which the haloperidol treatment dose could be escalated was left to clinicians and was neither protocolized or randomized. Ten percent of the patients with incident delirium never received treatment haloperidol although removal of these patients from the analysis did not change the results. Daily RASS scores were not available, and thus, we were not able to characterize daily delirium as hypoactive, hyperactive, or mixed. The haloperidol dose may have been more aggressively titrated upwards for patients with hyperactive (vs hypoactive) delirium. However, recent data suggest the association between haloperidol use in ICU patients with delirium and mortality is not driven by delirium subtype (29).

Although haloperidol used to prevent delirium in the REDUCE trial may have affected the haloperidol daily delirium treatment-mortality relationships we report, this relationship was consistent regardless of whether patients were randomized to the 1 mg, 2 mg, or placebo prevention arms. Although there are time-varying (e.g., daily changing severity of illness) and static factors (e.g. comorbidities) not included that could have influenced our analysis, days spent on mechanical ventilation (a useful marker for daily severity of illness) did not affect the results we report (14, 30). Importantly, the confounding variables we identified a priori are extensive and represent the key factors known to influence the relationship between delirium occurrence and mortality in critically ill adults, yet there may have been unmeasured confounders that we did not account for.

Although pharmacologic (e.g., choice of sedation) and nonpharmacologic (e.g., early mobilization) strategies known to affect delirium were not considered, our use of data from a rigorous clinical trial implies a similar distribution of these interventions across study sites and between treatment arms (12). Notably, centers reported 88% compliance with the use of nonpharmacologic delirium prevention methods. Additionally, inclusion of randomized treatment allocation did not alter the estimates of our models, suggesting a good balance of potential confounders and proper control within our analyses. We were unable to control for post-ICU factors that could affect the association between haloperidol exposure and mortality. These unmeasured factors could result in residual confounding influencing the mortality associations we report. Although haloperidol dose-escalation was delirium symptom-driven, the severity and types of symptoms present were not collected. It remains unclear if ICU

haloperidol exposure affects mortality more than 3 months after ICU admission. Our study was also not able to evaluate the association between the daily administration of more than 16 mg of haloperidol and mortality given daily doses this high were not permitted in the study. Last, the results of our analysis may not be fully extrapolatable at centers having ICU care processes different from those of our study.

CONCLUSIONS

Among patients without delirium at the time of ICU admission, the dose of haloperidol administered for the treatment of incident delirium and its symptoms, when it occurs, may be associated with improved survival. Future prospective trials are needed to confirm not only whether the treatment of symptomatic incident delirium in critically ill adults with haloperidol improves mortality but also whether it improves ICU survivorship. Nondelirium-related mechanisms for any potential haloperidol benefits also need to be clearly elucidated.

ACKNOWLEDGMENTS

We would like to acknowledge the Prophylactic Haloperidol Use for Delirium in ICU Patients at High Risk for Delirium Study Investigators for their help with data collection during the parent trial. They include Arjen J. C. Slooter, MD, PhD; Roger J. M. Brüggemann, PharmD, PhD; Lisette Schoonhoven, PhD; Albertus Beishuizen, MD, PhD; J. Wytze Vermeijden, MD, PhD; Danie Pretorius, MD; Jan de Koning, MD; Koen S. Simons, MD; Paul J. W. Dennesen, MD, PhD; Peter H. J. Van der Voort, MD, PhD; Saskia Houterman, PhD; Margaretha C. E. van der Woude, MD; Anna Besselink, MD; Lieuwe S. Hofstra, MD, PhD; Peter E. Spronk, MD, PhD; Walter van den Bergh, MD, PhD; Dirk W. Donker, MD, PhD; Malaika Fuchs, MD; Attila Karakus, MD, PhD; M. Koeman, MD, PhD; Mirella van Duijnhoven, MD; Gerjon Hannink, PhD.

1 *Department of Pharmacy and Health Systems Sciences, Bouve College of Health Sciences, Northeastern University, Boston, MA.*

2 *Department of Intensive Care, Radboud Institute for Health Science, Radboud University Medical Center, Nijmegen, The Netherlands.*

3 *Department of Health Sciences, Bouve College of Health Sciences, Northeastern University, Boston, MA.*

Supplemental digital content is available for this article. Direct URL citations appear in the printed text and are provided in the HTML and PDF versions of this article on the journal's website (http://journals.lww.com/ccmjournal).

Supported, in part, by ZonMw program Goed Gebruik Geneesmiddelen (dossier number 836031004). ZonMw had no role in the design and conduct of the study; collection, management, analysis, and interpretation of the data; preparation, review, or approval of the manuscript; and decision to submit the manuscript for publication.

Dr. Duprey's efforts are supported by the National Institute of Aging 1F31AG066460-01. Drs. Duprey, Devlin, Briesacher, and Saczynski received support for article research from the National Institutes of Health. Dr. Duprey disclosed off-label product use of haloperidol for delirium. Dr. van den Boogaard's institution received funding and support for article research from ZonMw. The remaining authors have disclosed that they do not have any potential conflicts of interest.

For information regarding this aticle, E-mail: j.devlin@neu.edu

REFERENCES

1. Slooter AJC, Otte WM, Devlin JW, et al: Updated nomenclature of delirium and acute encephalopathy: Statement of ten Societies. *Intensive Care Med* 2020; 46:1020–1022
2. Pandharipande PP, Girard TD, Jackson JC, et al; BRAIN-ICU Study Investigators: Long-term cognitive impairment after critical illness. *N Engl J Med* 2013; 369:1306–1316
3. Saczynski JS, Marcantonio ER, Quach L, et al: Cognitive trajectories after postoperative delirium. *N Engl J Med* 2012; 367:30–39
4. Wolters AE, van Dijk D, Pasma W, et al: Long-term outcome of delirium during intensive care unit stay in survivors of critical illness: A prospective cohort study. *Crit Care* 2014; 18:R125
5. Zaal IJ, Slooter AJ: Delirium in critically ill patients: Epidemiology, pathophysiology, diagnosis and management. *Drugs* 2012; 72:1457–1471
6. Ely EW, Gautam S, Margolin R, et al: The impact of delirium in the intensive care unit on hospital length of stay. *Intensive Care Med* 2001; 27:1892–1900
7. Collet MO, Caballero J, Sonneville R, et al; AID-ICU cohort study co-authors: Prevalence and risk factors related to haloperidol use for delirium in adult intensive care patients: The multinational AID-ICU inception cohort study. *Intensive Care Med* 2018; 44:1081–1089
8. Morandi A, Piva S, Ely EW, et al: Worldwide survey of the "assessing pain, both spontaneous awakening and breathing trials, choice of drugs, delirium monitoring/management, early exercise/mobility, and family empowerment" (ABCDEF) bundle. *Crit Care Med* 2017; 45:e1111–e1122
9. Girard TD, Pandharipande PP, Carson SS, et al; MIND Trial Investigators: Feasibility, efficacy, and safety of antipsychotics for intensive care unit delirium: The MIND randomized, placebo-controlled trial. *Crit Care Med* 2010; 38:428–437

10. Page VJ, Ely EW, Gates S, et al: Effect of intravenous haloperidol on the duration of delirium and coma in critically ill patients (Hope-ICU): A randomised, double-blind, placebo-controlled trial. *Lancet Respir Med* 2013; 1:515–523
11. Girard TD, Exline MC, Carson SS, et al; MIND-USA Investigators: Haloperidol and ziprasidone for treatment of delirium in critical illness. *N Engl J Med* 2018; 379:2506–2516
12. Devlin JW, Skrobik Y, Gélinas C, et al: Clinical practice guidelines for the prevention and management of pain, agitation/sedation, delirium, immobility, and sleep disruption in adult patients in the ICU. *Crit Care Med* 2018; 46:e825–e873
13. Marquis F, Ouimet S, Riker R, et al: Individual delirium symptoms: Do they matter? *Crit Care Med* 2007; 35:2533–2537
14. Klein Klouwenberg PM, Zaal IJ, Spitoni C, et al: The attributable mortality of delirium in critically ill patients: Prospective cohort study. *BMJ* 2014; 349:g6652
15. Duprey MS, van den Boogaard M, van der Hoeven JG, et al: Association between incident delirium and 28- and 90-day mortality in critically ill adults: A secondary analysis. *Crit Care* 2020; 24:161
16. Heymann A, Radtke F, Schiemann A, et al: Delayed treatment of delirium increases mortality rate in intensive care unit patients. *J Int Med Res* 2010; 38:1584–1595
17. van den Boogaard M, Slooter AJC, Brüggemann RJM, et al; REDUCE Study Investigators: Effect of haloperidol on survival among critically ill adults with a high risk of delirium: The REDUCE randomized clinical trial. *JAMA* 2018; 319:680–690
18. van den Boogaard M, Slooter AJ, Brüggemann RJ, et al: Prevention of ICU delirium and delirium-related outcome with haloperidol: A study protocol for a multicenter randomized controlled trial. *Trials* 2013; 14:400
19. Ely EW, Margolin R, Francis J, et al: Evaluation of delirium in critically ill patients: Validation of the confusion assessment method for the intensive care unit (CAM-ICU). *Crit Care Med* 2001; 29:1370–1379
20. Sessler CN, Gosnell MS, Grap MJ, et al: The richmond agitation-sedation scale: Validity and reliability in adult intensive care unit patients. *Am J Respir Crit Care Med* 2002; 166:1338–1344
21. Knaus WA, Draper EA, Wagner DP, et al: APACHE II: A severity of disease classification system. *Crit Care Med* 1985; 13:818–829
22. Luo L, Shaver CM, Zhao Z, et al: Clinical predictors of hospital mortality differ between direct and indirect ARDS. *Chest* 2017; 151:755–763
23. Szakmany T, Walters AM, Pugh R, et al: Risk factors for 1-year mortality and hospital utilization patterns in critical care survivors: A retrospective, observational, population-based data linkage study. *Crit Care Med* 2019; 47:15–22
24. Clermont G, Angus DC, Linde-Zwirble WT, et al: Does acute organ dysfunction predict patient-centered outcomes? *Chest* 2002; 121:1963–1971
25. Garland A, Olafson K, Ramsey CD, et al: Distinct determinants of long-term and short-term survival in critical illness. *Intensive Care Med* 2014; 40:1097–1105
26. Hill AB: The environment and disease: Association or causation? *Proc R Soc Med* 1965; 58:295–300
27. Poole D, Mayo PH, Møller MH: The wicked path of causal inference in observational studies. *Intensive Care Med* 2020; 46:799–801
28. Milbrandt EB, Kersten A, Kong L, et al: Haloperidol use is associated with lower hospital mortality in mechanically ventilated patients. *Crit Care Med* 2005; 33:226–269
29. Rood PJT, van de Schoor F, van Tertholen K, et al: Differences in 90-day mortality of delirium subtypes in the intensive care unit: A retrospective cohort study. *J Crit Care* 2019; 53:120–124
30. Wolters AE, Zaal IJ, Veldhuijzen DS, et al: Anticholinergic medication use and transition to delirium in critically ill patients: A prospective cohort study. *Crit Care Med* 2015; 43:1846–1852