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Association of Cumulative Dose of Haloperidol with Next Day Delirium in Older Medical Intensive Care Unit Patients

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Abstract

Objective—To evaluate the association between cumulative dose of haloperidol and next day diagnosis of delirium in a cohort of older MICU patients, with adjustment for its time dependent confounding with fentanyl and intubation.

Design—Prospective, observational study.

Setting—MICU at an urban, academic medical center

Patients—Age 60 and older admitted to the MICU who received at least one dose of haloperidol (N=93). Of these, 72 were intubated at some point in their MICU stay whereas 21 were never intubated.

Interventions—None

Measurements—Detailed data were collected concerning time, dosage, and route of administration of all medications, as well as for important clinical covariates, and daily status of intubation and delirium using the CAM-ICU and a chart-based algorithm.

Main Results—Among non-intubated patients, and after adjustment for time dependent confounding and important covariates, each additional cumulative milligram of haloperidol was associated with 5% higher odds of next day delirium with OR (CI) : 1.05 (1.02 – 1.09). After adjustment for time dependent confounding and covariates, intubation was associated with a five-fold increase in odds of next day delirium with OR (CI): 5.66 (2.70 – 12.02). Cumulative dose of haloperidol among intubated patients did not change their already high likelihood of next day delirium. After adjustment for time dependent confounding the positive associations between indicators of intubation and of cognitive impairment and next day delirium became stronger.

Conclusions—These results emphasize the need for more studies regarding the efficacy of haloperidol for treatment of delirium among older MICU patients and demonstrate the value of assessing non-intubated patients.

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Keywords

MICU; haloperidol; delirium; time-dependent confounding; marginal structural model; psychoactive; geriatric

Delirium is defined as an acute change in mental status with alteration in cognition and attention, which can fluctuate over time. Delirium is especially common in critically ill medical intensive care unit (MICU) patients with prevalence rates of 50-90% in older patients (1). Several studies have demonstrated that delirium in the ICU has been independently associated with increased mortality (2, 3), length of hospital stay (4), and increased hospitalization costs (5). In addition, many risk factors associated with the development of delirium have been identified, including advanced age, dementia, severity of illness, hypertension, active tobacco use, as well as metabolic disturbances (6, 7).

There are several lines of evidence to suggest that certain medications are also associated with delirium in MICU patients. In one study looking at older MICU patients, benzodiazepines prescribed prior to MICU admission was one of the strongest risk factors for delirium (8). In a separate study looking at mechanically ventilated adults admitted to medical or coronary intensive care units, even after adjusting for other medications and risk factors, lorazepam was an independent risk factor for transitioning to delirium (9). It has also been previously shown that use of benzodiazepines or opioids, after correcting for other factors, is independently associated with prolonged episodes of delirium in older patients (10). Prolonged delirium duration in turn leads to longer MICU stays and complications, such as greater risk for nosocomial infections, which contributes to longer stays and higher costs.

Although its efficacy has never been demonstrated in a randomized controlled trial, haloperidol is commonly used to treat the symptoms of delirium among older patients in the MICU (11). Because medication use is a potentially modifiable risk factor for delirium, we sought to evaluate the association between cumulative dose of haloperidol and next day delirium among older MICU patients that received haloperidol. Because there are often several medications being administered concurrently with interventions such as mechanical ventilation, it is important to adjust for confounding. Marginal structural models were introduced by Robins (12) to adjust for time-dependent confounding. In this longitudinal, observational study we construct a marginal structural model that weights each observation by its inverse probability of treatment for specific doses of haloperidol and fentanyl and for intubation, while adjusting for important clinical covariates.

Methods

Study Design

A prospective observational cohort of patients age 60 and older admitted to the MICU of Yale New Haven Hospital (YNHH). Exclusion criteria included inability to communicate prior to admission, non-English speaking, admitted to the MICU for less than 48 hours, admission from another intensive care unit, and lack of an identifiable proxy able to consent and provide background information. Of the 318 eligible patients, 309 patients were

enrolled. Of the 309 enrolled participants, 93 received at least one dose of haloperidol during their stay in the MICU. These 93 patients were followed from MICU admission through MICU discharge or for a maximum of eight days. This study was approved by the Institutional Review Board of Yale University School of Medicine and was assigned the protocol number 11888.

Patient Characteristics

After enrollment all patients had a proxy identified who was interviewed about their status prior to MICU admission. We utilized a proxy screen to determine the best respondent to answer questions about the patients' baseline health status (8). We collected baseline patient characteristics including demographic data, medical and psychiatric history, and outpatient medications. From the proxy interviews, data was collected to complete the Informant Questionnaire on Cognitive Decline in the Elderly (IQCODE) to screen for preexisting cognitive impairment (13). Patient charts were reviewed to calculate the Charlson Comorbidity Index (14) and Acute Physiology and Chronic Health Evaluation (APACHE II) scores (15). We recorded the presence of organ dysfunction as well as all ICU level interventions including the need for intubation and mechanical ventilation. Patients were assessed on a daily basis by a trained research nurse using the confusion assessment method for the ICU (CAM-ICU) to diagnose delirium. We supplemented these CAM-ICU interviews with a daily validated chart review (16). Patients were weighed upon admission to the MICU and their height was measured to calculate body mass index.

Detailed records of medication use were collected for all patients in the study, by nursing flow chart review, and through an automated pharmacy medication system. We collected data on the time, dose, and route of administration of all medications, beginning from either presentation at the emergency room or from the hospital floor prior to MICU admission. All routes of drug administration were included in our dosing calculation. For fentanyl these routes included transdermal and intravenous drug delivery, and for haloperidol and lorazepam, intravenous and oral routes.

Sedation Protocol and Practices in our MICU

During the time of study enrollment we did not have a set protocol for sedation, agitation or pain management. The majority of our patients received fentanyl for pain control and lorazepam for sedation, with a very small minority of patients receiving midazolam or propofol. At that time haloperidol was the only antipsychotic in routine use and there was no systematic use of any sedation awakening protocol.

Statistical Analysis

Justification for a Marginal Structural Model—A previous study based on this cohort reported positive associations between use of haloperidol and use of either a benzodiazepine or opioid and duration of delirium in the MICU (17). Because all intubated patients in that analysis received either benzodiazepine or opioid, a key limitation was its inability to separate the confounding effects of intubation and sedation on duration of delirium, including their time dependent confounding. An example of time dependent confounding is when the levels of treatment of the current day depend on the levels of covariates or parallel

treatments from the previous day. For example sedation is typically given to facilitate intubation, which is suspected of causing delirium, and which in turn is treated with haloperidol. These three interventions exhibit time dependent confounding. Because these three treatments were given to the MICU patients on a daily basis, i.e., intubation, sedation (benzodiazepines and or opioids), and haloperidol, it was important to control for the time dependent confounding among them. When such time dependent confounding is present, standard approaches for adjustment of confounding are biased (12). Marginal structural models (MSM) are a new class of model used with observational data to estimate the causal effect of a given time-dependent exposure, such as cumulative dose of haloperidol, in the presence of time-dependent covariates, e.g., intubation and sedation, that may serve simultaneously as confounders and intermediate variables (18-20).

Implementation of a Marginal Structural Model (MSM)—MSM allows for the removal of some of the time-varying covariates from the main outcome model. In our case, because the time-dependent causal information shared among the MICU interventions of the current day and the previous day's delirium is captured in weights calculated from separate models unique to each intervention, the current day's delirium status is not used to predict the likelihood of next day delirium. The far left of Figure 1 shows the weight models that calculate the likelihood of the given levels of haloperidol and fentanyl and use of intubation on the current day (t), by drawing information from the current (t) and previous (t-1) days. The probabilities generated from the models on the far left of Figure 1 are subsequently multiplied and utilized as weights in the outcome model, i.e., the MSM. The weights serve to create a pseudo-population of observations balanced in both time-invariant and time-varying covariates, that emulates randomization. Their use consequently facilitates the calculation of causal associations from simple repeated measures models such as the logistic regression used in this study (21). The outcome of the MSM is the likelihood of being diagnosed with delirium on the next day (t+1), conditional on the current day's interventions and the baseline covariates.

Sequence of Analytical Steps—Characteristics of our study sample were summarized with means and standard deviations or medians and interquartile ranges for continuous variables, and with counts and percentages for dichotomous variables.

In order to obtain data for our analysis, we calculated the total 24-hour doses of fentanyl, haloperidol, and lorazepam for each patient-day in the MICU through a maximum of eight days. Cumulative dose of lorazepam was not included in the final outcome model for two statistical reasons. Because our clinical practice uses both drugs simultaneously, doses of fentanyl and lorazepam were highly correlated, creating risk of collinearity in multivariable adjustment. Second, because the large majority of the lorazepam patient-doses were administered on days when patients were not receiving haloperidol, there was insufficient information to simultaneously calculate associations for both drugs. This is a meaningful limitation because lorazepam, the preferred sedative for intubation in our clinic, is also a known risk factor for delirium. For this reason we compared the demographic characteristics of the intubated and non-intubated subgroups and described the average cumulative doses administered to each.

Separate models were used to calculate the probability of treatment for the following treatments: cumulative dose of fentanyl, cumulative dose of haloperidol, and intubation. Because a large majority of the patient-days had zero doses of both fentanyl and haloperidol, the latter were modeled using a zero-inflated Poisson (ZIP) distribution that calculated the likelihood of receiving the specific dose on each patient-day (22, 23). Intubation was modeled with a logistic generalized estimating equation model that adjusted for the repeated daily measurements within each patient. Each of the three models of probability of treatment included adjustment for age in years, APACHE II score excluding the Glasgow Coma Scale (GCS), number of days in the MICU, delirium on the previous day, intubation on the previous day, preexisting cognitive impairment, male sex, nonwhite race, the cumulative doses of fentanyl and haloperidol through the previous day, and patient weight. The model to calculate weighting for intubation also included the cumulative dose of lorazepam dose through the previous day. Each model of probability of treatment yielded stabilized weights as defined by Robins (12) that were multiplied and subsequently inverted to yield a single composite inverse probability of treatment weight.

Finally, a Bayesian logistic model with an exchangeable correlation structure was used to calculate the multivariable associations between delirium on a given day and the following explanatory variables: baseline values of age, APACHE II score excluding the GCS, preexisting cognitive impairment, male sex, nonwhite race, patient weight, cumulative dose of fentanyl through previous day, cumulative dose of haloperidol through previous day, previous day's intubation status, and previous day's interaction between cumulative dose of haloperidol and intubation status. Each model term was assigned a non-informative normal prior distribution.

The multivariable associations between all model terms and delirium are presented as odds ratios (OR) with 95% credible intervals (CI), from both un-weighted and weighted models. A comparison of the results from the un-weighted and weighted models showed how sensitive the final results were to the weight modeling process.

Models were evaluated using SAS version 9.3 (24). Significance for all parameters was interpreted as a 95% credible interval that excluded the null value of one.

Results

The demographic data of our study population is presented in Table 1. Because our study group of patients taking haloperidol is a subset of the larger cohort, we do not report p-values for differences in key characteristics between the cohort of 309 and our analytical subset of 93. However, in Table 1 there are several notable differences. With regards to demographics there were fewer males (44% vs. 47%) and more persons admitted from home (81% vs. 78%) in the study subgroup than in the overall cohort. The patients taking haloperidol also had higher rates of baseline depressive symptoms (38% vs. 28%), preexisting cognitive impairment (41% vs. 31%), and impairment in activities of daily living (42% vs. 36%) than the overall cohort. More patients taking haloperidol were admitted with a diagnosis of respiratory failure (59% vs. 51%) and fewer with gastrointestinal hemorrhage (9% vs. 17%) than the overall cohort.

Characteristics of the MICU Stay

With respect to MICU stay in the overall cohort, more patients receiving haloperidol experienced delirium (100% vs. 79%) on at least one day and more were intubated (77% vs. 54%). Among patients taking haloperidol, median time on ventilation was higher (8 days vs. 6) as was median length of stay (8 days vs. 4) than in the overall cohort. Figure 2 shows the asymmetrical distribution of lorazepam use among patients taking haloperidol that precluded the concurrent calculation of associations for haloperidol and lorazepam. We observe that whereas 18% of intubated patients concurrently received haloperidol and lorazepam, only 9% of non-intubated patients concurrently received both.

Figure 3 presents the frequency distribution of the daily doses of haloperidol across the study sample. Nearly forty percent of the daily haloperidol doses were 6 milligrams or less and 93% were 30 milligrams or less.

A comparison of intubated and non-intubated patients showed that 72 were intubated at some point in their MICU stay and 21 were not. Comparing the demographics of intubated and non-intubated patients revealed several notable distinctions. Intubated patients were, on average, younger than non-intubated patients (73.9 years versus 76.4), more often female (59.7% versus 42.9%), more severely ill (average Apache score 25.1 versus 22.0), and more often reported depression (40.3% versus 28.6%). Relative to intubated patients, non-intubated patients were more often non-white (28.6% versus 12.5%), had more cognitive impairment (52.4% versus 37.5%), and were more often admitted for sepsis (28.6% versus 11.1%). Likely due to the small sample sizes, none of the aforementioned differences were statistically significant. The one statistically significant difference was expected in that many more of the intubated patients were admitted for respiratory illness (72.2% versus 14.3%).

Among the intubated, the average cumulative lorazepam doses for days 1 through 8 were, in milligrams, as follows: 4.8, 11.9, 20.0, 25.8, 31.9, 36.8, 44.1, and 49.9. Among non-intubated patients, the average cumulative doses for days 1 through 6 were, in milligrams, as follows: 0.8, 1.7, 3.2, 4.0, 4.7, and 6.7. There is no data for days 7 and 8 because none of the non-intubated patients in the MICU received lorazepam beyond day 6. We observe that the average cumulative dose of lorazepam among intubated patients is consistently around six times higher than that given to the non-intubated patients.

Multivariable Associations

Table 2 gives the multivariable associations between explanatory variables and subsequent delirium for both un-weighted and weighted models, where the latter are adjusted for the time-dependent confounding of the MICU treatments (cumulative doses of haloperidol and fentanyl and intubation status through prior day). The first three rows of results were generated from the main effects for cumulative dose of haloperidol and intubation status and their interaction, and are relative to non-intubated patient days when no haloperidol was taken. The first row states that among non-intubated patients, each additional milligram in the cumulative dose of haloperidol was positively associated with 5% higher odds of next day delirium: un-weighted OR (CI) of 1.06 (1.01-1.14) and weighted OR (CI) of 1.05 (1.02

– 1.09). The nearly complete overlap of the credible intervals of the weighted and unweighted results indicates that this association is not sensitive to the weight modeling process or to the time dependent confounding the weights seek to address. The second row indicates that intubated patients taking haloperidol have high odds of next day delirium with unweighted OR (CI) of 3.39 (1.61 – 8.01) and weighted OR (CI) of 5.48 (2.44 – 12.50). The stronger association from the weighted model suggests that the time-dependent confounding with cumulative drug doses masked some of the association between intubation and next day delirium. The large association in the second row must, however, be interpreted in the context of the third row. The third row, with unweighted OR (CI) of 3.38 (1.67 – 7.08) and weighted OR (CI) of 5.66 (2.70 – 12.02), tells us that intubated patients have, on average, nearly identical odds for next day delirium as the intubated patients taking haloperidol. We interpret the equivalent odds of next day delirium for intubated patients, regardless of haloperidol use, as meaning that any potential effect from cumulative dose of haloperidol is overpowered by the much stronger association between intubation and next day delirium. Any interpretation of the association with intubation must, however, acknowledge that our model confounds the effect of intubation with that of lorazepam.

The fourth row shows no association between cumulative dose of fentanyl and next day delirium in either model. Most notable among the covariates is the doubling in strength of the association between baseline cognitive impairment and next day delirium in going from an unweighted OR (CI) of 3.75 (1.67 – 8.17) to a weighted OR (CI) of 7.62 (3.72 – 16.06).

Discussion

To our knowledge this is the first study to evaluate the association between cumulative dosage of haloperidol and next day delirium among older patients in the MICU that rigorously accounts for the time-dependent confounding of sedation, intubation, and prior day delirium. Our results suggest that for critically ill non-intubated older patients, and after adjustment for important time-dependent confounders, haloperidol is associated with a small increase in the odds of next day delirium. Because many studies of delirium in the ICU have been restricted to intubated patients only (2), this study's result is novel and suggests a potential need to re-evaluate the use of haloperidol as a treatment for delirium among non-intubated patients in the ICU.

Whereas several studies have demonstrated a positive association between longer episodes of delirium and increased mortality (10, 25), a recent systematic review and meta-analysis of randomized ICU trials did not identify any association between reduced duration of delirium and short-term mortality (26). The current literature evaluating potential interventions for delirium consists of a number of small studies that are typically non-blinded. Apart from the obvious danger of contamination between treatment groups in a non-blinded study, these studies are likely underpowered to evaluate associations with delirium-related outcomes such as cognitive or functional decline and mortality. Larger studies are needed to demonstrate the efficacy of delirium interventions and to evaluate associations between reduced duration of delirium and these delirium-related outcomes.

Strengths of this study include adjustment for important baseline covariates such as baseline cognitive impairment and the use of a marginal structural model that draws on the well documented temporal ordering of the drug doses and daily evaluations of delirium. This model is designed to sort out the multiple levels of confounding between intubation, haloperidol, and fentanyl.

Because there are no randomized controlled trials that have evaluated haloperidol's efficacy for treating delirious patients in the MICU, the recent Society for Critical Care Medicine (SCCM) guidelines no longer recommend haloperidol for treatment of delirium in the MICU (27). To help address this gap in knowledge, the multi-site MIND-USA randomized controlled trial was designed to evaluate the efficacy of haloperidol for treatment of delirium among critically ill patients requiring ventilatory support for respiratory failure and vasopressors for sepsis (28). Interestingly, the doses of haloperidol administered in our study were much higher than the doses being used in the MIND-USA study, with the majority of our patients receiving more than 6mg per day. In this study we have not examined the impact of daily dose on next day delirium, and we speculate there may be a daily dose threshold of haloperidol, which, when exceeded, may be associated with prolongation of delirium. Our results suggest that haloperidol may not increase duration of delirium in patients who are concurrently intubated and receiving other psychoactive medications such as benzodiazepines. They also suggest the importance of studying the impact of haloperidol on delirium in MICU patients who do not require intubation.

Study Limitations

There are several study limitations that merit discussion. Because of the low amount of shared lorazepam and haloperidol use among our patients, we did not have enough information to separately estimate their respective associations. In light of the recent acknowledgement of the CAM-ICU's sensitivity to the use of sedatives (29), our exclusion of lorazepam represents a confounder that has not been rigorously addressed. This study, like most research conducted in the MICU, was observational. Observational studies are susceptible to imbalances in both measured and unmeasured covariates. Because haloperidol was given at the discretion of the treating physician we do not have indication for its use. In this subgroup all patients receiving haloperidol had delirium documented either by our research staff or in their medical record. While we made daily assessments for delirium status, we did not evaluate for the extra pyramidal side-effects of haloperidol. Because this was a single-center study of older MICU patients, additional studies are needed to replicate the modest association between cumulative dose of haloperidol and next day delirium reported here.

Conclusions

In our cohort we have demonstrated an association between cumulative dose of haloperidol and next day delirium among older, non-intubated MICU patients and replicated the previously identified associations between indicators of cognitive decline and intubation with subsequent delirium. Because our evaluation employed a marginal structural model that calculated inverse probability weights for cumulative doses of fentanyl (sedation) and

haloperidol (anti-psychotic), as well as intubation, it adjusted for time dependent confounding. These results point to the need for more studies regarding the efficacy of haloperidol for treating the symptoms of delirium among older MICU patients.

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Figure 1. Marginal Structural Model of Association between Cumulative Dosage of Haloperidol and Next Day Diagnosis of Delirium N=93 (persons receiving one or more doses of haloperidol during ICU stay)

Figure 2. Percent of Days Patients Received Haloperidol and/or Lorazepam

Figure 3. Daily Doses of Haloperidol during MICU Stay

Table 1
MICU Admission Characteristics of Patients

Characteristic	Entire Cohort (n=309) ^a	Haloperidol (n=93) ^b
Age in years, mean (SD)	74.7 (8.5)	74.4 (7.7)
Male, n (%)	145 (47)	41 (44)
Education in years, mean (SD)	12.5 (2.8)	12.5 (2.9)
Non-white race, n (%)	51 (17)	15 (16)
APACHE II score, mean (SD)	23.5 (6.4)	24.4 (6.0)
Charlson Co-Morbidity Index, mean (SD)	1.8 (1.9)	1.6 (1.6)
Admitted from home ^c , n (%)	241 (78)	75 (81)
Baseline Medical Status		
Evidence of depression ^d , n (%)	85 (28)	35 (38)
Dementia, n (%)	95 (31)	38 (41)
Any Impairment in Activities of Daily Living, n (%)	111 (36)	39 (42)
Admitting Diagnosis		
Sepsis, n (%)	51 (17)	14 (15)
Respiratory, n (%)	156 (51)	55 (59)
Neurologic, n (%)	5 (2)	3 (3)
Gastrointestinal hemorrhage, n (%)	52 (17)	8 (9)
Other, n (%)	45 (15)	13 (14)
MICU Factors		
Delirium during ICU Stay ^e , n (%)	239 (79)	93 (100)
Intubated, n (%)	167 (54)	72 (77)
Days of ventilation, Median (IQR)	6 (3-11)	8 (4-18)
Length of stay, Median (IQR)	4 (3-8)	8 (5-16)

^a Missing data present for some subjects. For Charlson Co-Morbidity missing=1; Dementia missing=3

^b Missing data present for some subjects. For Charlson Co-Morbidity missing=1

^c Admitted from home versus Skilled Nursing Facility or Rehabilitation Center

^d Evidence by surrogate or chart

^e Delirium by CAM interview or chart review during entire ICU stay

Table 2
Multivariable Associations with Diagnosis of Next Day Delirium, N=93^a

	Un-weighted Outcome (not adjusted for time dependent confounding)	Weighted Outcome ^b (adjusted for time dependent confounding)
Variables with Time Dependent Confounding ^c	Odds Ratio (95% CI) ^d	Odds Ratio (95% CI) ^d
Cumulative dose of haloperidol (mg) among non-intubated patients	1.06 (1.01 – 1.14)	1.05 (1.02 – 1.09)
Cumulative dose of haloperidol (mg) among intubated patients	3.39 (1.61 – 8.01)	5.48 (2.44 – 12.50)
Intubation	3.38 (1.67 – 7.08)	5.66 (2.70 – 12.02)
Cumulative dose of fentanyl (mg)	1.03 (0.98 – 1.09)	1.02 (0.95 – 1.12)
Covariates		
Age in years	0.96 (0.92 – 1.00)	0.93 (0.89 – 0.97)
Apache II less GCS	1.00 (0.94 – 1.06)	1.08 (1.03 – 1.13)
Cognitively impaired ^e	3.75 (1.67 – 8.17)	7.62 (3.72 – 16.06)
Male sex	1.28 (0.67 – 2.43)	0.71 (0.39 – 1.30)
Nonwhite race	0.29 (0.14 – 0.64)	0.37 (0.16 – 0.85)
Patient Weight in pounds	1.00 (0.99 – 1.00)	1.00 (1.00 – 1.01)

Abbreviations: CI: credible interval (Bayesian equivalent of confidence interval), GCS: Glasgow Coma Scale, mg: milligrams, iqcodeA: informative questionnaire on cognitive decline in the elderly

^aThe 93 participants contributed 598 patient-days of follow-up.

^bMarginal structural model with weighting for cumulative fentanyl, cumulative haloperidol, and intubation. Model weight was product of individual weights

^cEach variable with time dependent confounding measured on day preceding diagnosis of delirium

^dSignificance defined as credible interval exclusive of 1.00.

^eDefined as a score of 3.3 or lower on the iqcodeA