OBSERVATIONAL STUDY

OPEN

Association of Histamine-2 Blockers and Proton-Pump Inhibitors With Delirium Development in Critically Ill Adults: A Retrospective Cohort Study

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OBJECTIVES: Histamine-2 receptor antagonists are commonly administered for stress ulcer prophylaxis in critically ill adults and may be associated with delirium development. We aimed to determine differential associations of histamine-2 receptor antagonist or proton-pump inhibitor administration with delirium development in patients admitted to a medical ICU.

DESIGN: Retrospective observational study using a deidentified database sourced from the University of North Carolina Health Care system. Participants were identified as having delirium utilizing an *International Classification of Diseases*-based algorithm. Associations among histamine-2 receptor antagonist, proton-pump inhibitor, or no medication administration and delirium were identified using relative risk. Multiple logistic regression was used to control for potential confounders including mechanical ventilation and age.

SETTING: Academic tertiary care medical ICU in the United States.

PATIENTS: Adults admitted to the University of North Carolina medical ICU from January 2015 to December 2019, excluding those on concurrent histamine-2 receptor antagonists and proton-pump inhibitors in the same encounter.

INTERVENTIONS: None.

MEASUREMENTS AND MAIN RESULTS: We identified 6,645 critically ill patients, of whom 29% ($n = 1,899$) received mechanical ventilation, 45% ($n = 3,022$) were 65 or older, and 22% ($n = 1,487$) died during their medical ICU encounter. Of the 6,645 patients, 31% ($n = 2,057$) received an histamine-2 receptor antagonist and no proton-pump inhibitors, 40% ($n = 2,648$) received a proton-pump inhibitor and no histamine-2 receptor antagonists, and 46% ($n = 3,076$) had delirium. The histamine-2 receptor antagonist group had a greater association with delirium than the proton-pump inhibitor group compared with controls receiving neither medication, after controlling for mechanical ventilation and age (risk ratio, 1.36; 1.25–1.47; $p < 0.001$) and (risk ratio, 1.15; 1.07–1.24; $p < 0.001$, respectively).

CONCLUSIONS: Histamine-2 receptor antagonists are more strongly associated with increased delirium than proton-pump inhibitors. Prospective studies are necessary to further elucidate this association and to determine if replacement of histamine-2 receptor antagonists with proton-pump inhibitors in ICUs decreases the burden of delirium in critically ill patients.

KEY WORDS: critical care; delirium; histamine H2 antagonists; mechanically ventilated; older adults; proton-pump inhibitors

Delirium is an acute decline in cognitive function associated with multiple adverse outcomes such as an increased fall risk, prolonged hospital stay, and a two- to three-fold increased risk of death (1–3).

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Delirium is frequently encountered in the ICU setting, with older ICU patients facing the highest disease burden, for whom delirium rates are as high as 80% (1). Medications are a common inciting factor for delirium development and are responsible for 12–39% of cases (4). As delirium is often resolved upon cessation of the inciting medication, it is critical to identify potentially risky medications, especially those that are commonly prescribed.

An estimated 70% of patients admitted to ICUs receive proton-pump inhibitors (PPIs) and histamine-2 receptor antagonists (H2RAs) for stress ulcer prophylaxis (5). H2 receptor antagonism in the brain can dampen neural cholinergic stimulation and adversely affect arousal, wakefulness, and attention to cause delirium (6, 7). Anti-histaminergic effects of H2RAs should be localized to the gastric mucosa; however, H2 receptors are also widely distributed in the brain, creating the potential for delirium precipitation in elderly patients with compromised blood-brain barriers (6, 8–10). In studies of long-term hospitalized patients, H2RAs have been associated with variable rates of CNS symptoms such as psychosis, agitation, hallucinations, mental status changes, and disorientation, with rates ranging from 1.6% to 80% (6, 11–14).

Prior retrospective studies have demonstrated greater prevalence of delirium in critically ill patients taking H2RAs rather than PPIs and have reported reduced delirium severity after patients taking H2RAs were switched to PPIs (15–19). These studies are limited in number and have low generalizability due to strict inclusion criteria and small sample size. We sought to better characterize the association between delirium and medications commonly used for stress ulcer prophylaxis in a large, heterogeneous ICU sample.

MATERIALS AND METHODS

Setting and Design

We conducted a retrospective, observational study using the Informatics for Integrating Biology and the Bedside (i2b2) to gather patient data from January 2015 to December 2019. i2b2 is a self-service way for researchers to examine patient cohorts by querying the Carolina Data Warehouse for Health (CDW-H). The CDW-H is a central data repository containing clinical, research, and administrative data sourced from the University of North Carolina (UNC) Health Care System. Researchers can apply criteria for patient demographics, encounter information, *International Classification of Diseases*, 9th Revision (ICD-9) and *International Classification of Diseases*, 10th Revision diagnoses, ICD-9 procedure codes, vitals, laboratory results, and medications. In response to a query, i2b2 returns the number of patients matching the search criteria. No patient identifiers or clinical data are revealed in the result set.

The Institutional Review Board (IRB) at the UNC at Chapel Hill (UNC-CH) waived approval and informed consent due to the aggregated level of the data (IRB No. 20-1073).

Study Population and Cohort Definition

Deidentified patient data from the UNC-CH i2b2 database was queried to include all critically ill patients admitted to the UNC-CH Memorial Hospital Medical ICU (UNCMH MICU) during the study period. UNCMH is a large tertiary care center with an active 30-bed MICU. This ICU is well-versed in delirium assessment and management. The UNC-CH MICU was one of the study centers for the Modifying the Impact of ICU-Associated Neurological Dysfunction study and The Society of Critical Care Medicine's ICU Liberation Bundle Project. The Confusion Assessment Method for the ICU is the standard delirium assessment method in the UNCMH MICU, and it is performed at least once per nursing shift (every 12 hr).

Participants were excluded if they had dual use of both H2RAs and PPIs during their hospitalization, as this reflects a unique population and was unlikely to represent those receiving routine care. Eligibility was not limited to any specific medical indications for either H2RA or PPI use. Participants were 18 and older. Mechanical ventilation was screened for using CPT codes 5A1935Z, 5A1945Z, and 5A1955Z. Death during hospitalization was identified using discharge dispositions of "expired" or "expired in medical facility." We also collected data on routine patient demographics such as age, race, ethnicity, and sex.

The H2RA group was defined as having no PPI use and having one or more instances of administration of the following medications: famotidine, cimetidine, ranitidine, and nizatidine. The PPI group was defined as having no H2RA use and having one or more instances

of administration of the following medications: dexlansoprazole, esomeprazole, esomeprazole/naproxen, pantoprazole, rabeprazole, lansoprazole, omeprazole, magnesium hydroxide/omeprazole/sodium bicarbonate, omeprazole/sodium bicarbonate. The control cohort was comprises patients with no instances of either PPI or H2RA administration (**Fig. 1**).

Outcomes

We defined delirium development based on the algorithm delineated by Kim et al (20), in which a set of specific ICD codes was found to best capture delirium diagnosis in a retrospective analysis of electronic medical records. Presence of one or more instances of any of these codes was used as a marker for delirium (**Table S1**, Supplemental Digital Content, http://links.lww.com/CCX/A750). i2b2 queries were structured such that administration of the medication of interest had to occur in the same encounter (MICU stay) as delirium development. Cohort grouping methods are outlined in Figure 1. H2RA and PPI groups were further stratified by individual medication to assess for differences in delirium associations between single agents.

Statistical Analysis

Statistical analysis was conducted using Stata statistical software (Release 16; StataCorp LLC, College Station, TX). Descriptive statistics were used to report basic demographic characteristics of the entire cohort. We collapsed age into a dichotomous variable with those less than 65 years old versus those 65 years and older. We conducted a univariate binomial regression to obtain the relative risk of delirium development among patients on H2RAs compared with controls. We also conducted within-group univariate regressions to examine the associations of age and mechanical ventilation with delirium. This was repeated for the PPI group. We then conducted univariate analyses to examine whether any individual PPI might be more associated with delirium than another. We also compared delirium development among those on H2RAs compared with those on PPIs, excluding control patients not on medications, in a univariate binomial regression. Lastly, we conducted multivariate modified Poisson regressions to examine the associations of H2RAs or PPIs with delirium, controlled for patient characteristics found to be significantly associated with delirium in the previous univariate regressions.

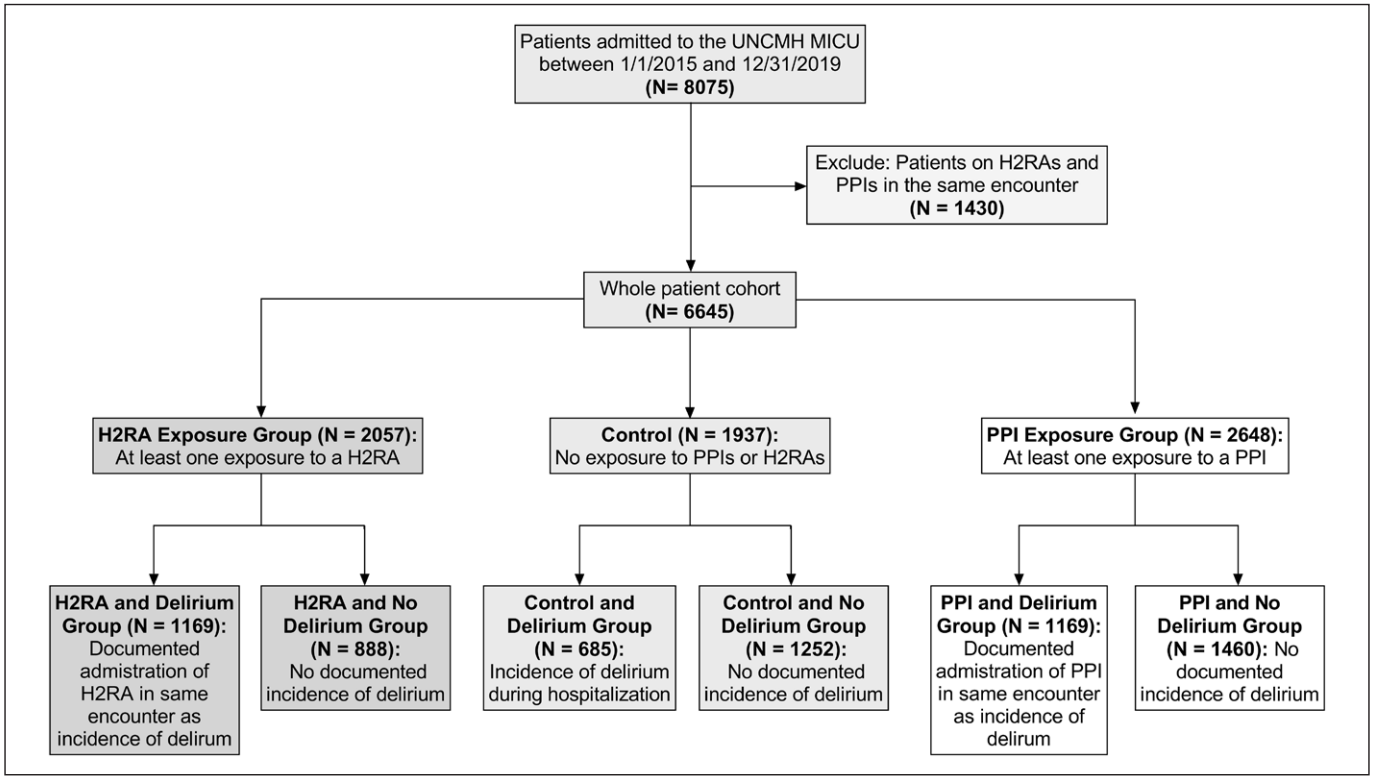

Figure 1. Flow diagram of patient cohort selection in Informatics for Integrating Biology and the Bedside. H2RA = histamine-2 receptor antagonist, MICU = medical ICU, PPI = proton-pump inhibitor, UNCMH = University of North Carolina at Chapel Hill Memorial Hospital.

We also conducted a stratified analysis by any patient characteristic that changed the risk ratio (RR) of either an H2RA or PPI with delirium by more than 10% upon addition to the multivariate model. *p* values less than 0.01 were considered statistically significant.

RESULTS

Cohort Characteristics

Between January 2015 and December 2019, 8,075 adults were admitted to the UNC-CH MICU. Of these patients, 6,645 were included in the cohort after removal of the 1,430 patients prescribed both H2RAs and PPIs in the same hospital encounter. In the remaining cohort, 45% (*n* = 3,022) were 65 or older, 29% (*n* = 1,899) received mechanical ventilation, and 22% (*n* = 1,487) died during their MICU encounter. Of the 6,645 patients, 31% (*n* = 2,057) received an H2RA and no PPIs, 40% (*n* = 2,648) received a PPI and no H2RAs, and 46% (*n* = 3,076) had a delirium diagnosis (**Table 1**). Over 99% of patients (*n* = 2,048) who received H2RAs were prescribed famotidine. Of those who received a PPI, 70% (*n* = 1,839) were prescribed pantoprazole and 20% (*n* = 517) were prescribed omeprazole. The remainder were prescribed esomeprazole (1%, *n* = 14) and other PPIs.

Group Characteristics: Age, Mechanical Ventilation, and Mortality Among the H2RA and PPI Groups

Patients on H2RAs were less likely to be 65 or older compared with those on PPIs or those on neither medication (41% [95% CI, 39–43%] vs 50% [48–52%] and 44% [42–46%], respectively) (Table 1). However, patients on H2RAs had higher inhospital mechanical ventilation rates (54% [52–56%] vs 24% [22–26%] or 8% [7–9%], respectively) and higher inhospital mortality rates than patients on PPIs or control patients on neither drug (27% [25–29%] vs 23% [21–24%] or 16% [14–18%], respectively).

Association of Group Characteristics and H2RA and PPI Use With Delirium in Unadjusted Analysis

Patients 65 or older had a small but statistically significantly higher relative risk of delirium than younger patients (RR, 1.07; 1.02–1.13; $p = 0.008$). Mechanical ventilation was significantly associated with increased delirium compared with nonmechanically ventilated patients (RR, 1.69; 1.61–1.78; $p < 0.001$). The risk of delirium was significantly higher in the H2RA group and the PPI group than controls (RR, 1.61; 1.50–1.73;

TABLE 1.
Cohort Characteristics

Cohort Characteristics	Entire Cohort, *n* = 6,645, *n* (%)	Control Group, *n* = 1,937, *n* (%)	Histamine-2 Receptor Antagonist Group, *n* = 2,057, *n* (%)	Proton-Pump Inhibitor Group, *n* = 2,648, *n* (%)
Female	3,224 (49)	1,051 (50	1,016 (49)	1,220 (46)
Race				
White or Caucasian	3,956 (60)	1,096 (57)	1,187 (58)	1,671 (63)
Black or African American	1,925 (29)	579 (30)	640 (31)	706 (27)
Other/unknown	621 (9)	211 (11)	186 (9)	221 (8)
Age				
18–44	1,257 (19)	478 (25)	466 (23)	315 (12)
45–64	2,363 (36)	601 (31)	748 (36)	1,014 (38)
65 and above	3,022 (45)	857 (44)	843 (41)	1,319 (50)
Mechanical ventilation	1,899 (29)	157 (8)	1,109 (54)	633 (24)
Deceased during hospitalization	1,487 (22)	309 (16)	559 (27)	596 (23)
Delirium	3,076 (46)	685 (35)	1,169 (57)	1,188 (45)

$p < 0.001$) and (RR, 1.27; 1.18–1.37; $p < 0.001$, respectively). Risk of delirium was significantly higher in the H2RA group than that in the PPI group (RR, 1.27; 1.20–1.34; $p < 0.001$).

Association of Group Characteristics and H2RA and PPI Use With Delirium in Adjusted Analysis

We built two multivariate models to assess the association of medication administration (either H2RA or PPI), age, and ventilation status with delirium. Within the H2RA model in the adjusted analysis, H2RA use, older age, and mechanical ventilation were significantly associated with delirium development (RR, 1.35; 1.25–1.47; $p < 0.001$), (RR, 1.19; 1.11–1.26; $p < 0.001$), and (RR, 1.44; 1.33–1.55; $p < 0.001$, respectively) (**Table 2**). In the adjusted PPI models, PPI use, older age, and mechanical ventilation were significantly associated with delirium development (RR, 1.15; 1.07–1.24; $p < 0.001$), (RR, 1.11; 1.03–1.19; $p = 0.003$), and (RR, 1.65; 1.54–1.78; $p < 0.001$, respectively) (**Table 3**). Risk of delirium was significantly higher in the H2RA group than that in the PPI group (RR, 1.10; 1.04–1.17; $p = 0.001$).

When stratifying by individual PPIs given and controlling for mechanical ventilation and age, pantoprazole was significantly associated with delirium development, whereas omeprazole was not (RR, 1.15; 1.06–1.24; $p = 0.001$) and (RR, 1.00; 0.89–1.14; $p = 0.93$, respectively). In both of the multivariate analyses, after adjusting for older age, the risk of delirium in patients on either H2RAs or PPIs did not change significantly, or by more than 10% of their unadjusted value. Thus, age was not a significant confounder of the association between H2RA or PPI use and delirium. However, the risk of delirium in patients on either H2RAs or PPIs changed significantly after adjusting for mechanical ventilation, suggesting the presence of confounding.

Stratification by Ventilation Status

When patient groups were stratified by ventilation status to account for confounding, mechanically ventilated patients on H2RAs or on PPIs had significantly greater associations with delirium compared with ventilated controls on neither medication (RR, 1.41; 1.19–1.67; $p < 0.001$) and (RR, 1.40; 1.17–1.67; $p < 0.001$, respectively) (**Fig. 2**). However, no significant difference in ventilated patients was present between H2RA and PPI associations with delirium when compared to each other (RR, 1.01; 0.94–1.08; $p = 0.81$).

In the nonmechanically ventilated patient set, patients on H2RAs had significant associations with delirium compared with nonventilated controls (RR, 1.33; 1.21–1.46; $p < 0.001$). Patients on PPIs did not have a significant association with delirium (RR, 1.12; 1.02–1.21; $p = 0.012$). In nonventilated patients, H2RAs had significantly greater associations with delirium

TABLE 2.
Relative Risk of Delirium Development by Cohort Characteristics on Histamine Blockers ($n = 2,057$)

Cohort Characteristics	Delirium, *n* (%)	No Delirium, *n* (%)	Unadjusted RR (95% CI)	*p*	Absolute Difference, %	Adjusted RR (95% CI)[a]	*p*
H2RA[b] ($n = 2,057$)	1,169 (57)	888 (43)	1.61 (1.50–1.73)	< 0.001	22	1.35 (1.25–1.47)	< 0.001
Proton-pump inhibitor/H2RA control ($n = 1,937$)	685 (35)	1,252 (65)					
≥ 65 yr old ($n = 843$)	504 (60)	339 (40)	1.17 (1.10–1.25)	< 0.001	5	1.18 (1.11–1.26)	< 0.001
< 65 yr old ($n = 1,214$)	665 (55)	549 (45)					
Mechanically ventilated ($n = 1,109$)	737 (66)	372 (34)	1.68 (1.57–1.78)	< 0.001	20	1.44 (1.33–1.55)	< 0.001
Not ventilated ($n = 948$)	432 (46)	516 (54)					

H2RA = histamine-2 receptor antagonist, RR = risk ratio.

[a]Adjusted for mechanical ventilation and age.

[b]Compared with control group.

TABLE 3.
Relative Risk of Delirium Development by Cohort Characteristics on Proton-Pump Inhibitors (*n* = 2,648)

Cohort Characteristics	Delirium, *n* (%)	No Delirium, *n* (%)	Unadjusted RR (95% CI)	*p*	Absolute Difference, %	Adjusted RR (95% CI)[a]	*p*
PPI[b] (*n* = 2,648)	1,188 (45)	1,460 (55)	1.26 (1.18–1.37)	< 0.001	10	1.15 (1.07–1.24)	< 0.001
PPI/histamine-2 receptor antagonist control (*n* = 1,937)	685 (35)	1,252 (65)					
≥ 65 yr old (*n* = 1,319)	574 (44)	745 (56)	1.10 (1.02–1.17)	0.010	2	1.11 (1.03–1.86)	0.003
< 65 yr old (*n* = 1,329)	614 (46)	715 (54)					
Mechanically ventilated (*n* = 633)	417 (66)	216 (34)	1.71 (1.59–1.83)	< 0.001	28	1.65 (1.54–1.78)	< 0.001
Not ventilated (*n* = 2,015)	771 (38)	1,244 (62)					

PPI = proton-pump inhibitor, RR = risk ratio.
[a]Adjusted for mechanical ventilation and age.
[b]Compared with control group.

than PPIs, contrasting with the previous finding in ventilated patients (RR, 1.19; 1.09–1.30; $p < 0.001$).

DISCUSSION

In this retrospective observational cohort study of MICU patients, we found that H2RAs were more strongly associated with increased risk of delirium than PPIs. Overall, 46% of our MICU cohort developed delirium, in agreement with previous studies, where the rate of delirium in ICUs has been reported to range from 20% to 80% (1, 2, 21). Mechanical ventilation and increased age also demonstrated a significant association with delirium, in accordance with prior literature (22). The association between H2RAs and delirium was most significant for those not mechanically ventilated.

In nonventilated patients, those on H2RAs had a statistically significant 12% absolute increase in delirium development compared with those receiving no medications. Those on PPIs had a nonsignificant 4% increase in the frequency of delirium. Given the lack of treatments for delirium, the ability to reduce the incidence of delirium by over 10% might represent an important opportunity for reducing the morbidity and mortality seen in ICUs.

In the UNCMH MICU, indications for stress ulcer prophylaxis include mechanical ventilation greater than 48 hours, coagulopathy, severe trauma or burn, renal or liver failure, septic shock, extracorporeal membrane oxygenation, or major operative procedures including transplants (23, 24). UNC treatment guidelines indicate the use of H2RAs as the first-line drugs for stress ulcer prophylaxis. PPIs are second-line drugs and are administered to higher risk patients. Concern for potential confounding by indication was lessened by the fact that H2 blockers were prescribed to lower risk patients but were still more significantly associated with delirium than PPIs.

Our main finding mirrored the overall conclusion of other smaller studies found in the literature search that characterized H2RA use, PPI use, and delirium. In a prospective study of 21 Japanese hepatectomized recipients, patients were randomized to treatment with either famotidine or omeprazole for postoperative ulcer management. The incidence rates and severity of delirium were significantly higher in the famotidine group (90%) than the omeprazole group (27.3.%) (odds ratio, 3.82; 1.15–12.71; $p < 0.01$) (18). The second study retrospectively studied rates of delirium in 60 postsurgical esophageal cancer patients treated with either H2RAs or PPIs for ulcer prevention. The incidence of delirium was significantly higher in the H2RA group (43.3%) than the PPI group (16.7%) ($p = 0.047$). Additionally, in the 11 patients from the H2RA group who developed delirium, switch from an H2RA to a PPI reduced delirium severity (19).

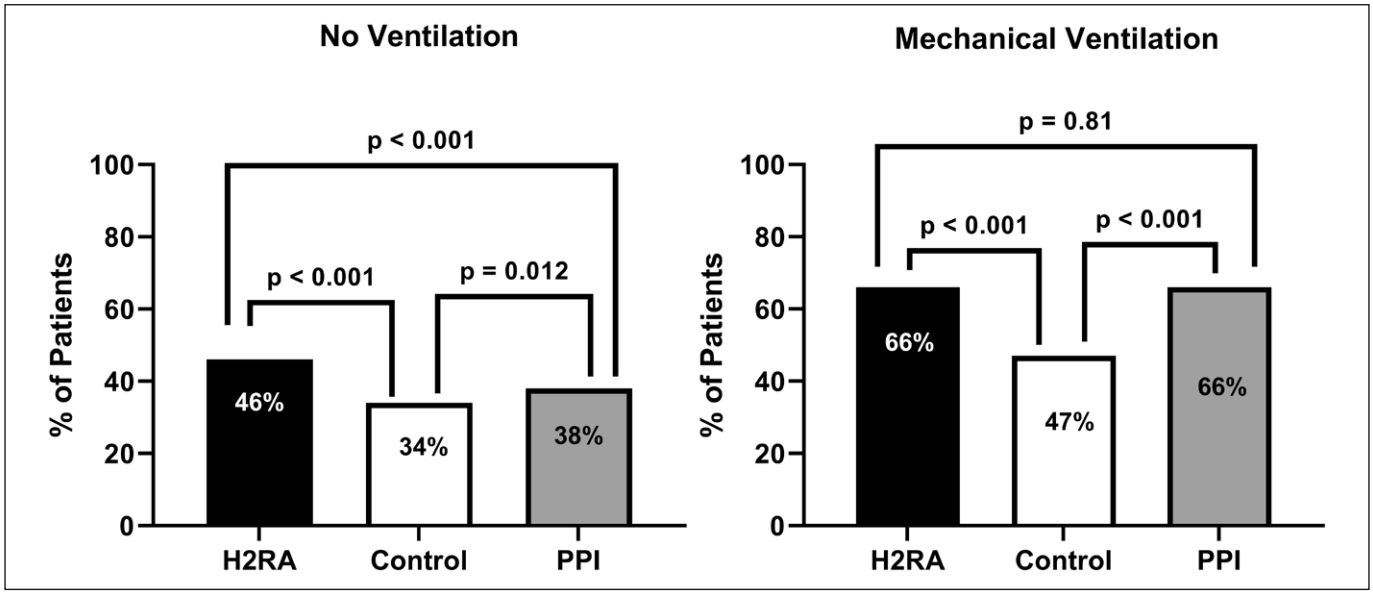

Figure 2. Percent of patients developing delirium in relation to type of medication administered, stratified by ventilation status. H2RA = histamine-2 receptor antagonist, PPI = proton-pump inhibitor.

Compared with these studies, our analysis had a much larger sample size, fewer exclusion criteria, and controlled for potential confounders such as mechanical ventilation. These differences could account for the discrepancy in absolute percentages of delirium; in our cohort, 57% of patients on H2RAs developed delirium, compared with 45% of patients on PPIs. Unlike the aforementioned studies, ours also used nonmedicated control groups to generate RRs. Future clinical trials may be needed to determine the benefits of switching from an H2RA to a PPI in critically ill patients for delirium prevention.

In our mechanically ventilated patient group, both H2RAs and PPIs were associated with an increased risk of delirium development, and there was no statistically significant difference in the delirium risk between H2RAs and PPIs. This suggests an underlying mechanism of delirium related to ventilation or medications taken during ventilation. Studies have postulated that mechanical ventilation can increase the permeability of the blood-brain barrier (25). Furthermore, mechanically ventilated patients usually have a higher medication burden than nonventilated patients (26). Potential deliriogenic effects of H2RAs or PPIs could be outweighed by these factors relating to mechanical ventilation; this finding points to a need for further research.

Further work will need to examine the risk-benefit ratio of H2RAs versus PPIs, including delirium risk. In the United States overall, PPIs are prescribed more widely than H2RAs for hospitalized patients (27–29). Prior literature concerning the differential efficacy of the agents for upper gastrointestinal bleed prophylaxis is conflicting, and studies suggest that PPIs are associated with higher rates of pneumonia and *Clostridium difficile* infection, as well as increased healthcare costs (28, 30). Compared with PPIs, H2RAs demonstrate greater rates of tachyphylaxis (31).

This study's strengths include a large sample size and limited exclusion criteria. This study also has important limitations. This was a retrospective, observational single-site study, meaning that causation could not be established, and generalizability is limited. Furthermore, we were unable to assess the temporal relationships between events using i2b2. We could not establish the order of medication administration, ventilation, and delirium development within a hospitalization. Additionally, association strength may have increased as a patient requiring H2RAs or PPIs may have had other risk factors that predisposed them to delirium, independent of the medications themselves. These potential confounders include use of deliriogenic medications, comorbidities such as prior gastrointestinal pathology, and prior delirium diagnoses. To minimize bias, we adjusted for age and ventilation status, two of the most contributory risk factors to delirium development. Finally, though we used the currently most thoroughly vetted set of ICD and antipsychotic codes

to abstract a delirium diagnosis, this algorithm was shown to identify delirium with a sensitivity of 30%, a specificity of 97%, and a positive predictive value of 83% (20). Furthermore, this algorithm showed higher sensitivity for hyperactive or mixed delirium (64%) and severe delirium (73%). Due to this, our study may have under-abstracted delirium diagnoses, especially milder or hypoactive delirium cases.

CONCLUSIONS

In a large, retrospective study of 6,645 critically ill adults, H2RA exposure was more strongly associated with delirium than PPI exposure. This association could be limited by underlying confounders outside the scope of the study design, as the database used could not abstract delirium subtypes or relevant comorbidities, nor establish a temporal association. Prospective studies are necessary to further elucidate this association, eliminate confounders, and determine if replacement of H2RAs with PPIs in ICUs decreases the burden of delirium in high-risk patients.

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