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BRIEF COMMUNICATIONS

Famotidine Use Is Associated With Improved Clinical Outcomes in Hospitalized COVID-19 Patients: A Propensity Score Matched Retrospective Cohort Study

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See Covering the Cover synopsis on page 803.

Keywords: Coronavirus 2019; SARS-CoV-2; Famotidine; Histamine-2 Receptor Antagonists.

Coronavirus Disease 2019 (COVID-19) caused 2 million cases and more than 150,000 deaths worldwide as of mid-April 2020.[1] Clinical trials are under way to assess the efficacy of a variety of antiviral drugs; however, many of these drugs have toxicities and thus far no drug has been proven to improve outcomes in patients with COVID-19.

Famotidine is a histamine-2 receptor antagonist that suppresses gastric acid production. In vitro, famotidine inhibits human immunodeficiency virus replication.[2] Recently, Wu et al.[3] used computational methods to predict structures of proteins encoded by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) genome and identified famotidine as one of the drugs most likely to inhibit the 3-chymotrypsin-like protease ($3CL^{pro}$), which processes proteins essential for viral replication.[4] We hypothesized that famotidine would be associated with improved clinical outcomes among hospitalized patients with COVID-19. To explore this, we performed a retrospective cohort study at a single academic center located at the epicenter of the COVID-19 pandemic in the United States.

Methods

Complete methods are available in the Supplementary Materials. In brief, adults were eligible for the study if they were admitted to our institution from February 25, 2020, to April 13, 2020, and tested positive for SARS-CoV-2 within no more than 72 hours following admission. Patients were excluded if they died or were intubated within 48 hours following hospital admission. The primary exposure was use of famotidine (any dose, form of administration, or duration), classified as present if famotidine was received within 24 hours of hospital admission and otherwise as absent. The primary outcome was a composite of death or endotracheal intubation from hospital day 2 to day 30 (intubation-free survival). This follow-up period avoided immortal time bias because the exposure was classified based on the 24-hour period after hospitalization and the at-risk period began on hospital day 2. Cox proportional hazards modeling was performed on the full cohort, and a matched subset was examined with propensity scoring matching to balance baseline characteristics based on use of famotidine.

Results

Population and Use of Famotidine

A total of 1620 patients met criteria for analysis, including 84 patients (5.1%) who received famotidine within 24 hours of hospital admission. Home use of famotidine was documented on admission medication reconciliation in 15% of those who used famotidine while hospitalized compared with 1% of those who did not ($P < .01$). Twenty-eight percent of all famotidine doses were intravenous; 47% were 20 mg, 35% were 40 mg, and 17% were 10 mg. Famotidine users received a median 5.8 days of drug for a total median dose of 136 mg (63–233 mg). There were minimal differences comparing patients who used famotidine with those who did not, and balance between the groups was further improved after propensity score matching (Supplementary Table 1).

Death or Intubation

A total of 142 (8.8%) patients were intubated and 238 (15%) died; 340 (21%) patients met the composite study outcome. In crude analysis, use of famotidine was significantly associated with reduced risk for the composite outcome of death or intubation (Figure 1*A*, log-rank $P < .01$). This association was driven primarily by the relationship between famotidine and death (Figure 1*B*, log-rank

Abbreviations used in this paper: **CI, confidence interval; COVID-19, Coronavirus Disease 2019; PPI, proton pump inhibitor; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2.**

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Reading development in a tracked school system: A longitudinal study over 3 years using propensity score matching

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Background. Assigning students to different school tracks on the basis of their achievement levels is a widely used strategy that aims at giving students the best possible learning opportunity. There is, however, a growing body of literature that questions such positive effects of tracking.

Aims. This study compared the developmental trajectories of reading comprehension and decoding speed between students at academic track schools that typically prepare students for university entrance and students at non-academic track schools that usually prepare students for vocational education.

Sample. In a longitudinal design with three occasions of data collection, the authors drew on a sample of $N = 1{,}508$ 5th graders (age at T1 about 11 years, age at T3 about 14 years) from 60 schools in Germany. The academic track sample comprised $n = 568$ students; the non-academic track sample comprised $n = 940$ students.

Method. Achievement measures were obtained by standardized tests of reading comprehension and decoding speed. Students at the different tracks were closely matched using propensity scores. To compare students' growth trajectories between the different school tracks, we applied multi-group latent growth curve models.

Results. Comparable results were recorded for the complete (unmatched) sample and for the matched pairs. In all cases, students at the different tracks displayed a similar growth in reading comprehension, whereas larger growth rates for students at academic track schools were recorded for decoding speed.

Conclusions. Our findings contribute to an increasing body of literature suggesting that tracking might have undesired side effects.

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Emulating a Novel Clinical Trial Using Existing Observational Data

Predicting Results of the PreVent Study

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Abstract

Rationale: "Target trial emulation" has been proposed as an observational method to answer comparative effectiveness questions, but it has rarely been attempted concurrently with a randomized clinical trial (RCT).

Objectives: We tested the hypothesis that blinded analysts applying target trial emulation to existing observational data could predict the results of an RCT.

Methods: PreVent (Preventing Hypoxemia with Manual Ventilation during Endotracheal Intubation) was a multicenter RCT examining the effects of positive-pressure ventilation during tracheal intubation on oxygen saturation and severe hypoxemia. Analysts unaware of PreVent's results used patient-level data from three previous trials evaluating airway management interventions to emulate PreVent's eligibility criteria, randomization procedure, and statistical analysis. After PreVent's release, results of this blinded observational analysis were compared with those of the RCT. Difference-in-differences estimates for comparison of treatment effects between the observational analysis and the PreVent trial are reported on the absolute scale.

Results: Using observational data, we were able to emulate PreVent's randomization procedure to produce balanced groups for comparison. The lowest oxygen saturation during intubation was higher in the positive-pressure ventilation group than the no positive-pressure ventilation group in the observational analysis ($n = 360$; mean difference = 1.8%; 95% confidence interval [CI] = −1.0 to 4.6) and in the PreVent trial ($n = 401$; mean difference = 3.9%; 95% CI = 1.4 to 6.4), though the observational analysis could not exclude no difference. Difference-in-differences estimates comparing treatment effects showed reasonable agreement for lowest oxygen saturation between the observational analysis and the PreVent trial (mean difference = −2.1%; 95% CI = −5.9 to 1.7). Positive-pressure ventilation resulted in lower rates of severe hypoxemia in both the observational analysis (risk ratio = 0.60; 95% CI = 0.38 to 0.93) and in the PreVent trial (risk ratio = 0.48; 95% CI = 0.30 to 0.77). The absolute reduction in the incidence of severe hypoxemia with positive-pressure ventilation was similar in the observational analysis (9.4%) and the PreVent trial (12.0%), though the difference between these estimates had wide CIs (mean difference = 2.5%; 95% CI = −8.0 to 13.6%).

Conclusions: Applying target trial emulation methods to existing observational data for the evaluation of a novel intervention produced results similar to those of a randomized trial. These findings support the use of target trial emulation for comparative effectiveness research.

Keywords: clinical trials; intubation; epidemiology; causal inference; target trial emulation

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*A complete list of members of the Pragmatic Critical Care Research Group Investigators may be found in the online supplement.

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