EDITORIAL

Proton Pump Inhibitors vs Histamine-2 Receptor Blockers for Stress Ulcer Prophylaxis in Critically Ill Patients

Issues of Interpretability in Pragmatic Trials

Todd W. Rice, MD, MSc; Sunil Kripalani, MD, MSc; Christopher J. Lindsell, PhD

Among critically ill patients in the intensive care unit (ICU), complications are frequent, including stress ulcers in the upper gastrointestinal tract. To help prevent the development of ulcers, antagonism of gastric acid (with antacids historically) or inhibition of the production of acid (with histamine-2 receptor blockers more recently) were implemented as part of routine critical care. The introduction of proton pump inhibitors, with data demonstrating improved ulcer prevention and recovery compared with histamine-2 receptor blockers in non-critically ill patients, led many physicians who provide care for critically ill patients to incorporate proton pump inhibitors for routine stress ulcer prophylaxis.[1] However, the lack of randomized clinical trials (RCTs) that directly compared histamine-2 receptor blockers with proton pump inhibitors for stress ulcer prophylaxis in critically ill patients, combined with decreasing incidence of significant gastrointestinal bleeding in these patients and emerging evidence of an association between proton pump inhibitor use and adverse events, including *Clostridioides difficile (Clostridium difficile)* infection,[2] cognitive decline,[3] and nosocomial pneumonia,[4] made the optimal choice of routine stress ulcer prophylaxis less clear.

Related article

In this issue of *JAMA,* the PEPTIC Investigators[5] report the results of a large international open-label, registry-embedded pragmatic RCT that compared 2 different stress ulcer prophylaxis strategies in critically ill adults receiving invasive mechanical ventilation, with the option for the treating physician to override the recommended choice and switch the patient to the nonpreferred strategy. The trial enrolled 26 828 patients over 30 months and used a cluster crossover design, in which 50 ICUs were assigned to either histamine-2 receptor blockers or proton pump inhibitors as the recommended prevention strategy for an initial 6 months and then the ICUs were crossed over to the other strategy for a subsequent 6 months.

Patients were expected to preferentially receive the study-assigned prevention strategy, although the assigned strategy was overridden a considerable proportion of the time, with 1 in 5 patients in the histamine-2 receptor blocker group receiving proton pump inhibitors, and 1 in 20 patients in the proton pump inhibitor group receiving histamine-2 receptor blockers. Overall, the 90-day in-hospital mortality (18.3% in the proton pump inhibitor group vs 17.5% in the histamine-2 receptor blocker group) difference between the 2 strategies did not achieve statistical significance, although the lower bound of the 95% CI for the risk ratio equaled 1 (1.00-1.10). This finding precludes the possibility of benefit of recommending proton pump inhibitors as the default stress ulcer prophylaxis strategy for reducing mortality, but also may suggest the possibility that the proton pump inhibitor prophylaxis strategy increased mortality.

Although the trial was powered for a difference of 2.4% in 90-day mortality, the smaller difference of 0.8% would be meaningful, if real, given that hundreds of thousands of critically ill patients are at risk annually. This would be the case even given that fewer patients assigned to receive the proton pump inhibitor strategy experienced clinically important upper gastrointestinal bleeding (1.3% vs 1.8% in the histamine-2 receptor blocker group; risk ratio, 0.73; P = .009), presumably from decreased incidence of stress-related mucosal bleeding. Newly acquired *C difficile* infections did not differ significantly between treatment strategies, nor did duration of mechanical ventilation and ICU and hospital lengths of stay. Together, these data would suggest an absolute increase in mortality of 0.8% with a decreased incidence in gastrointestinal bleeding of 0.5%, and might prompt clinicians to conclude that, at the population level, a strategy of avoiding proton pump inhibitors in favor of histamine-2 receptor blockers could result in reduced mortality, but at the cost of increased gastrointestinal bleeding. Such a conclusion, however, comes with some further considerations.

Pragmatic effectiveness trials are increasingly being used to compare different routinely used practices in critical care.[6] These designs introduce several potential benefits, including increased trial efficiency, facilitation of enrollment of large cohorts, and ability to generate evidence relevant to the actual practice environment. These trials also have numerous limitations, particularly when attempting to differentiate population effects from individual patient effects. Although the pragmatic, cluster crossover design of the PEPTIC (Proton Pump Inhibitors vs Histamine-2 Receptor Blockers for Ulcer Prophylaxis Treatment in the Intensive Care Unit) trial facilitated rapid enrolment of a large number of patients, features of this design introduced complexity in the understanding of the drug effects of proton pump inhibitors vs histamine-2 receptor blockers, as opposed to the understanding of the effects of deploying a strategy of recommending one drug instead of the other.

A particular risk to interpreting any RCT is when a meaningful proportion of patients do not receive the intended treatment. This risk can be exacerbated in pragmatic open-label trials that test different treatment strategies in which clinicians

are aware of and allowed to override study treatment assignment, thus diminishing fidelity to the intended strategy. In the PEPTIC trial,[5] 20% of patients in the histamine-2 receptor blocker group received proton pump inhibitors for stress ulcer prophylaxis. Although this may be presumed to bias the results toward finding no between-group differences, the likely nonrandom override of the recommend prevention strategy could have several effects. If patients at greatest risk of benefit or harm from one strategy had the recommended approach overridden in such a way that they all ended up receiving the same drug, any signal of either benefit or harm of the drug would be attenuated.

Moreover, the motivation for the trial was based on safety concerns of proton pump inhibitors, not a hypothesized benefit of histamine-2 receptor blockers. As such, this direction of bias should raise concerns. The potential indication bias introduced by clinicians lacking equipoise and treating higher-risk patients with proton pump inhibitors, even in the histamine-2 receptor blocker group, might have masked higher mortality from proton pump inhibitors and attenuated the benefit of a proton pump inhibitor strategy on clinically important upper gastrointestinal bleeding. The post hoc analyses by treatment adherence (in eTable 68 of the PEPTIC trial[5]) refute this, but the true effects of the specific drugs, as opposed to treatment strategies, in this trial cannot be disentangled due to the significant rate of override.

This potential bias is reinforced by the method of data collection. The PEPTIC trial[5] used a highly efficient registry-embedded approach. Although this approach decreases the time and resource burden on study personnel and increases the pragmatism of the trial, it also limits patient-level data collection and leaves numerous questions unanswered. If overriding the preferred drug biased the mortality signal to the null and proton pump inhibitors really do increase mortality, the limited scope of the data would preclude understanding the mechanism. It has been hypothesized that proton pump inhibitors might increase the risk for infections through potential inhibition of natural killer cells and immunosuppression,[7] but without data in the current trial by the PEPTIC trial investigators[5] on antibiotic administration or incident infections, these factors cannot be assessed. The observed differential treatment effect, whereby greater mortality risk for proton pump inhibitors was observed among more severely ill patients, might be argued to provide circumstantial evidence. Without an obvious mechanistic explanation, the potential mortality signal should be interpreted with caution.

The method of data collection limits the ability to disentangle heterogeneity of treatment effects. In the context of bidirectional effects (ie, proton pump inhibitors may contribute to mortality risk but also limit bleeding risk), clinicians may want to know which patients experienced increased mortality with proton pump inhibitors and compare that with which patients had decreased bleeding risk. If there are obvious differences, then perhaps clinicians could target proton pump inhibitor prophylaxis to avoid use in patients who had increased mortality risk and prioritize use in the patients who demonstrated reduced bleeding risk.

The presented exploratory data suggest that a proton pump inhibitor prophylaxis strategy might increase the risk of death among more severely ill patients (eTables 61-68 in the PEPTIC trial[5]), but not among those with less severe illness, while having a similar beneficial reduction in gastrointestinal bleeding across all illness severities (Table 3 in the article). However, the strength of this finding is undermined by not knowing which drug was actually provided to each patient, which is unfortunate given that one of the biggest strengths of large pragmatic comparative effectiveness RCTs is adequate sample size to rigorously evaluate differential treatment effects among different patient demographics and populations.[8]

One reason for selecting a cluster design is when important data are only available at the cluster level. For example, infection data are often available for an entire hospital unit, and not necessarily at the level of each individual patient. In the PEPTIC trial,[5] cases of *C difficile* infection were collected by cluster. Although the authors report that 40 patients in ICUs assigned the proton pump inhibitor strategy compared with 57 patients in ICUs assigned the histamine-2 receptor blocker strategy developed *C difficile*, it remains unknown which specific patients developed the infections or the duration of follow-up for detection. When combined with limited knowledge of which stress ulcer prophylaxis method was actually used in which specific patients, a true understanding of how proton pump inhibitors affect the incidence of *C difficile* cannot be ascertained. Collecting data at the level of the cluster reduces the granularity needed to translate group effects to the care of individual patients.

In conclusion, the PEPTIC trial investigators[5] provide extensive data that directly compared histamine-2 receptor blocker and proton pump inhibitor strategies for stress ulcer prophylaxis in patients requiring mechanical ventilation in the ICU. Enrolling more than 25 000 patients in 30 months in an RCT is a remarkable accomplishment. Overall, the results do not preclude the possibility of a small increase in hospital mortality with the proton pump inhibitor prophylaxis strategy despite showing a small, statistically significant reduction in clinically important gastrointestinal bleeding. Moreover, in the PEPTIC trial,[5] the large pragmatic open-label cluster crossover design with incomplete data on which patients in the trial received which drug confounds interpretation of the results and leaves the clinician unsure of the best way to optimize benefit and avoid harm when deciding on stress ulcer prophylaxis for individual critically ill patients.

ARTICLE INFORMATION

Author Affiliations: Division of Allergy, Pulmonary, and Critical Care Medicine, Department of Medicine, Vanderbilt University Medical Center, Nashville, Tennessee (Rice); Division of General Internal Medicine and Public Health, Department of Medicine, Vanderbilt University Medical Center, Nashville, Tennessee (Kripalani); Center for Clinical Quality and Implementation Research, Vanderbilt University Medical Center, Nashville, Tennessee (Kripalani, Lindsell); Department of Biostatistics, Vanderbilt University Medical Center, Nashville, Tennessee (Lindsell).

Corresponding Author: Todd W. Rice, MD, MSc, Division of Allergy, Pulmonary, and Critical Care Medicine, Vanderbilt University Medical Center, T-1218 MCN, Nashville, TN 37232 (todd.rice@vumc.org).

Published Online: January 17, 2020. doi:10.1001/jama.2019.22436

Conflict of Interest Disclosures: Drs Rice, Kripalani, and Lindsell are supported by the Vanderbilt Institute for Clinical and Translational Research Learning Healthcare System Platform under Clinical and Translational Science Award UL1 TR002243 from the National Center for Advancing Translational Sciences. Dr Rice reported receiving personal fees from Cumberland Pharmaceuticals. Dr Lindsell reported receiving grants from the National Institutes of Health, the Centers for Disease Control and Prevention, and the Marcus Foundation; and receiving personal fees from Endpoint Health.

REFERENCES

1. Krag M, Perner A, Wetterslev J, et al; SUP-ICU co-authors. Prevalence and outcome of gastrointestinal bleeding and use of acid suppressants in acutely ill adult intensive care patients. *Intensive Care Med*. 2015;41(5):833-845. doi:10.1007/s00134-015-3725-1

2. Kuehn BM. Reflux drugs linked to *C difficile*–related diarrhea. *JAMA*. 2012;307(10):1014. doi:10.1001/jama.2012.233

3. Gomm W, von Holt K, Thomé F, et al. Association of proton pump inhibitors with risk of dementia: a pharmacoepidemiological claims data analysis. *JAMA Neurol*. 2016;73(4):410-416. doi:10.1001/jamaneurol.2015.4791

4. Herzig SJ, Howell MD, Ngo LH, Marcantonio ER. Acid-suppressive medication use and the risk for hospital-acquired pneumonia. *JAMA*. 2009;301(20):2120-2128. doi:10.1001/jama.2009.722

5. The PEPTIC Investigators for the Australian and New Zealand Intensive Care Society Clinical Trials Group, Alberta Health Services Critical Care Strategic Clinical Network, and the Irish Critical Care Trials Group. Effect of stress ulcer prophylaxis with proton pump inhibitors vs histamine-2 receptor blockers on in-hospital mortality among ICU patients receiving invasive mechanical ventilation: the PEPTIC randomized clinical trial [published online January 17, 2020]. *JAMA*. doi:10.1001/jama.2019.22190

6. Semler MW, Self WH, Wanderer JP, et al; SMART Investigators and the Pragmatic Critical Care Research Group. Balanced crystalloids versus saline in critically ill adults. *N Engl J Med*. 2018;378(9):829-839. doi:10.1056/NEJMoa1711584

7. Capodicasa E, De Bellis F, Pelli MA. Effect of lansoprazole on human leukocyte function. *Immunopharmacol Immunotoxicol*. 1999;21(2):357-377. doi:10.3109/08923979909052768

8. Cook AJ, Delong E, Murray DM, Vollmer WM, Heagerty PJ. Statistical lessons learned for designing cluster randomized pragmatic clinical trials from the NIH Health Care Systems Collaboratory Biostatistics and Design Core. *Clin Trials*. 2016;13(5):504-512. doi:10.1177/1740774516646578