Reviewer
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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.

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, Young PJ, Bagshaw SM, Forbes AB, Nichol AD et al. *JAMA*. 2020; 323(7): 616-626.

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Context
This article describes the PEPTIC trial that sought to compare the mortality difference, if any, between using proton pump inhibitors (PPIs) and histamine-2 receptor blockers (H2RBs) in stress ulcer prophylaxis for adults requiring invasive mechanical ventilation. Even as this PEPTIC trial seeks to contribute to the scarcity of available mortality data on the two classes of stress ulcer prophylaxis drugs, the literature remains unclear on the best class of drug regarding efficacy and associated morbidity. A recent meta-analysis[1] of randomized clinical trials demonstrated that PPIs were better than H2RBs in preventing upper gastrointestinal bleeding. However, this meta-analysis was limited by a paucity of available data, methodological limitations of the trials analyzed and the possibility of publication bias. Furthermore, several studies[2-4] have implicated the increased use of PPIs with a greater risk for nosocomial pneumonia and *Clostridioides difficile* infection when compared to H2RBs. Therefore, in addition to the primary outcome of in-hospital mortality, secondary outcomes for the PEPTIC study included incidence of upper gastrointestinal bleeding, Clostridioides difficile infection, and ICU and hospital length of stay.

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Methods
- International (Canada, Ireland, England, Australia, and New Zealand) open-label randomized study (1:1 ratio), cluster crossover randomized clinical trial comparing PPIs vs H2RBs for stress ulcer prophylaxis.
- 50 ICUs (25 each arm) over a 30-month study period from August 2016 to January 2019.
- Inclusion criteria: patients 18 years old or older requiring invasive mechanical ventilation within 24 hours of admission to the ICU.
- Exclusion criteria: patients admitted to the ICU for an upper gastrointestinal (GI) bleed
- Each of the 2 cohorts would use as a default either the PPI or H2RB for stress ulcer prophylaxis, respectively, for a 6-month period then crossover to use the other drug class for a second 6-month period. (The intensivist reserved the right to override the default stress ulcer prophylaxis.)
- Duration of study treatment would be until death, development of an upper GI bleed ICU discharge, or stress ulcer prophylaxis determined not to be needed anymore.

- Different data collection methods for Canada and Ireland where data was collected individually at patient-level in real time, whereas, for the remaining countries data was collected from the medication chart of the 1st day of each month.
- The primary outcome was all-cause mortality at 90 days during index hospitalization up to 90 days after index ICU admission.
- The secondary outcomes included: 1) clinically important upper GI bleed*; 2) Clostridioides difficile infection; 3) ICU and hospital length of stay (LOS)
- The study was powered for a mean cluster period size of 310 patients with 80% power with a 2-sided significance level of 0.05 to detect an absolute reduction of 2.4% in-hospital from a baseline mortality of 15%, corresponding to a relative risk reduction of 16%.

*****A clinically important bleed in this study was defined by any of the following: hematemesis, melena, frank blood in the nasogastric tube or on upper endoscopy.

Findings

- Total of 26, 828 patients enrolled with 13,436 in the PPI arm and 13, 392 in the H2RB arm.
- Both cohorts similar in baseline characteristics with a mean age of 58 and mean APACHE II scores of 18.7.
- There was an overall total of 9691 female (36.1%), 8815 (32.9%) elective surgery, 4946 (18.4%) emergency surgery patients.
- 6,846 (50.9%) and 6915 (51.6%) surgery patients in the PPI and H2RB arms, respectively.
- The median ICU time (or exposure to drug class) was 2.8 and 2.7 days, for the PPI and H2RB arms, respectively.
- In the PPI arm 82.5% of patients received PPIs only, 4.1% H2RBs only, 1.9% both drugs, and 11.5% received neither.
- In the H2RB arm 63.6% of patients received H2RBs only, 20.1% PPIs only, 5.1% both drugs, and 11.2 % neither.
- There was an 18.3% mortality rate in the PPI. When compared with the H2RB mortality rate of 17.5% there was ***no*** statistical significance (RR, 1.05 [95% CI, 1.00 to 1.10]; absolute risk difference, 0.93 percentage points [95% CI, -0.01 to 1.88 percentage points]; p=0.054).
- There was a statistically significant lower incidence of upper GI bleeding in the PPI arm (1.3%) vs. the H2RB arm (1.8%). (RR, 0.73 [95% CI, 0.57 to 0.92]; absolute risk difference, -0.51 percentage points [95% CI, -0.90 to -0.12 percentage points]; p= .009).
- There was a lower incidence of Clostridioides difficile infection in the PPI arm (0.30%) vs. the H2RB arm (0.43%) but it did not reach statistical significance. (RR, 0.74 [95% CI, 0.51 to 1.09]; absolute risk difference, -0.11 percentage points [95% CI, -0.25 to 0.03 percentage points]; p=.13).
- There was no difference between both arms regarding ICU and hospital length of stay.

Commentary

This large randomized study did not demonstrate a statistically significant difference in 90-day mortality between use of PPI vs H2RB for stress ulcer prophylaxis in mechanically ventilated patients. In fact, it showed that there was an increased mortality (18.3%) in the PPI cohort as compared to the H2RB (17.5%). Albeit not statistically significant this mortality difference is arguably clinically significant. Especially, when one considers 2.5% of all ICU admissions will developed an upper GI bleed and to prevent this complication 70% of those patients will be put on stress ulcer prophylaxis[5]. Notably, this increased mortality trend in the PPI patients remained in subgroup analysis. For example, in those

patients who had cardiac surgery the RR for mortality was 1.27 (95% CI, 1.04-1.57). Additionally, alarming is the fact that over 20% of the H2RB cohort received PPIs and not H2RB stress ulcer prophylaxis. Clinicians were allowed to override the default intervention and may have chosen PPIs over H2RB because of a perceived efficacy advantage; however, a question might be raised as to whether a possible bias for PPI may have masked or attenuated a true and larger mortality difference between PPIs and H2RBs? In other words, if there were less PPI patients in the H2RB group would the study have shown a more robust mortality advantage associated with H2RBs? (The editorial by Rice TW et al.[6] elegantly dissects this notion.) Finally, in a post hoc subgroup analysis of illness severity quartiles, the cohort randomized to PPI in the two sickest quartiles (APACHE II score ranges 18-23 and 24-61, respectively) had an associated increased mortality when compared to their H2RB counterparts (p=.004). In sum, there seems to be a signal that PPIs may be associated with increased mortality.

Regarding the secondary endpoints, there was a clear advantage to using PPIs over H2RBs in reducing the incidence of clinically important upper GI bleeding with stress ulcer prophylaxis. This finding is consistent with the meta-analysis by Alhanazzi W et al.[1] On the other hand, this study did not demonstrate the possible link between PPIs and Clostridioides difficile infections. New-onset Clostridioides infection diagnoses were not significantly different between both cohorts (p=.13). PPIs have been implicated in increasing the risk of nosocomial pneumonias; unfortunately, this study did not add new information in that specific area. The study did not demonstrate any difference in ventilator time (hours) or ventilator-associated conditions (information only available from 8 Canadian ICUs) between the two cohorts. One may speculate that if PPIs do have some association with increased risk of nosocomial pneumonia it is likely mild to negligible given there is no difference in ventilator time or ventilator-associated conditions between both cohorts.

Implications for practice

Whether the association between PPIs and increased mortality is a real phenomenon, directly caused by PPIs, or is part of a separate but related unknown entity will require further study. That said, based on this study's findings the clinician should consider exercising more caution than before in using PPIs over H2RBs for stress ulcer prophylaxis in mechanical ventilated patients who may already be at increased risk of mortality. Perhaps, the specific group one should be cautious with are those patients with APACHE II scores above 18. For less sick patients according to the results of this study, PPIs should likely be the first choice in preventing upper GI bleeding without fear of increased Clostridioides difficile infections or, possibly, clinically severe nosocomial pneumonias. Lastly, given this study was done with over 50 percent surgery patients, these management suggestions may be more easily applied to our surgical ICU population.

References

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