

The End-Game for Pantoprazole in ICU? Not so fast...

O fim do jogo para Pantoprazol na UTI? Não tão rápido...

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The use of Proton Pump Inhibitors (PPIs) such as gastrointestinal bleeding prophylaxis (GIB) is a common practice in the world. However, there is no consistent evidence to demonstrate the reduction of mortality related to this practice. The article herein analysed (SUP-ICU), which had the objective of evaluating the reduction of mortality related to this prophylaxis, had a negative result. Despite the result presented, we can have another interpretation when we analyze the data more carefully.

The article entitled "Pantoprazole in Patients at risk for Gastrointestinal Bleeding in the ICU", published in NEJM in October 2018 by SUP-ICU group, is a randomized, blind, placebo-controlled, multicenter European study aimed to evaluate the effect of prophylactic Pantoprazole in patients at high risk for gastrointestinal bleeding (GIB) in patients admitted to the ICU. The hypothesis of the study was that the use of prophylactic pantoprazole would be associated with a lower incidence of gastrointestinal bleeding, but with higher rates of nosocomial infections and myocardial ischemia, when compared to the placebo group.

The protocol has previously been inserted into the site ClinicalTrials.gov under number NCT02467621 and published in 2016². The study was funded by the Innovation Fund Denmark, which had no role in the design or conduct of the project. There was no commercial support for the project.

This analysis aims to evaluate the result presented by the article regarding the scientific truth and its applicability in clinical practice.

By evaluating the pre-test probability of the study, we realized that the hypothesis is plausible. Since the 1990s, studies have shown the benefit of using Proton Pump Inhibitors (PPIs) in preventing GIB. It is known that GIB is associated with worsening of the results, including mortality. Patients on mechanical ventilation, patients with coagulopathy, hepatic or renal failure would be at greater risk of bleeding. Although widely used, there is no strong evidence to support the routine use of prophylactic PPIs, even in patients considered to be at high risk. In addition to the doubts about the benefits, there are doubts about the potential harmful effects, mainly related to increased incidence of infections by *Clostridium difficile* and myocardial ischemia.

The rationale for the study demonstrated to be adequate, with sufficient substantiating biological plausibility positive result.

This study, however, had a negative result. In the evaluation of a negative study we should look for some points in the analysis, among them the size of the sample, which generates low statistical power, or even inappropriate use of the treatment. It is precisely here that we have one of the primary points of this study. The intervention analyzed was not a treatment but a prophylaxis. It is known that prophylaxis can reduce mortality by reducing a serious illness.

In the protocol it was pre-specified that the difference between the groups should be $p < 0.05$ in order to be considered significant (avoid Type I error). It was decided that statistical power, in order to avoid Type II error, would be 90%. For this, a sample of 3350 participants was calculated to detect a 5% difference in mortality, considering a mortality in the control group of 25%, with a consequent reduction of the relative risk of 20%.

The inclusion criteria were adult patients admitted to the ICU, with at least one risk factor for severe GIB, including shock, use of anticoagulants, hemodialysis, mechanical ventilation for more than 24 hours, liver disease history and coagulopathy.

Exclusion criteria were contraindication to the use of PPIs, patients on previous treatment with PPIs or H2 receptor antagonists (H2RA), any SGI during hospitalization prior to randomization, patients undergoing organ transplants, palliative care or brain death, women pregnant and patient without due consent, according to the rules of the country of the participating center. All the mentioned criteria, of inclusion and exclusion, were well defined in pag. 62-64 of the Research Protocol³.

The randomization was central, with computer-generated order with stratified allocation by center. Well-conducted randomization avoids confounding effects. Patients were randomized to receive Pantoprazole 40mg intravenously diluted in NS 10ml once daily or placebo (NS 10ml) qid until discharge from the ICU. Patients were enrolled from 33 European ICUs, most of Denmark being

the headquarters of the SUP-ICU study group, from January 2016 to October 2017. There were small differences between the groups regarding patients with chronic respiratory diseases, coagulopathy and emergency surgeries. There were small differences between the groups regarding patients with chronic respiratory diseases, coagulopathy and emergency surgeries. It is important to note that the enteral diet, recognized as a protective factor of gastric mucosa lesion, was started on day 1 in 58.2% of the intervention group and 56.4% of the placebo group (Table S3, Appendix⁴). Based on Table 1 of the article, we can observe that the included patients actually had high severity (SAPS III between 48-49, SOFA score 9), which justified the high mortality in the groups.

The study was adequately masked. All samples were prepared, stored and distributed to participating centers (Figure S1, Appendix⁴). The primary outcome was mortality at 90 days, on an intention-to-treat basis. As an exploratory analysis, per protocol analysis was performed, but these results were not published in the original article. Violations of the protocol were very low, of 2.7% in all, equally distributed among the groups (Table S2, Appendix⁴). Excessive violations and cross-over are factors that could explain false negatives, but in this study there appears to be no significant impact on outcomes. Secondary outcomes were major gastrointestinal haemorrhage (defined as obvious bleeding associated with at least 1 of the 4 signs below: drop in systolic, diastolic, or mean pressure greater than 20mmHg, onset of vasopressor or 20% increase in previous dose, drop in Hb by at least 2g / dl, or transfusion of 2 or more red blood cells), new pneumonia, Clostridium difficile infection, severe adverse events or acute myocardial ischemia (STEMI, non-ST-segment elevation acute myocardial infarction, or unstable angina defined by the clinical picture and necrosis markers high). The criteria for defining secondary events are well defined on pages 7-9 of the Appendix⁴.

In the analysis of the screening, selection and randomization criteria of the participants, shown in figure 1, there is agreement with the criteria of the Consort Guidelines⁵. Follow-up of participants at an appropriate rate and low cross-over between groups, which strengthens the power of the study.

Regarding the results, the authors adequately fulfilled the scientific precept and answered the question of the primary objective: there was no statistically significant difference between the intervention and placebo groups. In presenting the data of secondary outcomes, as pre-defined in the protocol, no adjustments were made for multiple comparisons and no value of these analyzes was presented. The results of secondary endpoints and subgroups should be analyzed as hypothesis generators and by the principle of multiple tests even a spurious result could arise with a significant difference between the groups. To avoid this risk the authors did not make such analyzes.

Considering the presented data, we can conclude that the study was properly designed, presented and conducted. Your results should be considered true.

The question of the necessity of "death" outcome in a study of this complexity is questioned. Although this outcome is exempt from questioning about its importance, critical patients are often very complex and the chance of an isolated intervention to reduce mortality in this context is very low. As mentioned above, if we consider that intervention is a prophylaxis, and as such the chance of it having a significant impact on mortality is even lower. This study was negative for the primary outcome. However, even with all the limitations of an analysis of this size, considering the secondary outcomes, there was reduction of gastrointestinal bleeding, with a relative risk reduction of 0.58 (95% CI 0.40 - 0.86). This generates a NNT (number needed to treat) of 58 patients (for desfeche of obvious gastrointestinal bleeding), ie, we would need to treat 58 patients to avoid one obvious GIB.

The discussion regarding the choice of the primary outcome of this study should be considered. The use of the death outcome has the great advantage of being considered a hard, definitive outcome, without questioning the diagnosis. This is the most relevant outcome. But in interventions such as the one performed in this study, mortality becomes distant from the immediate impact of therapy, which is the reduction of GIB. In the ICU setting, with extremely severe patients (mortality in around 30%) it becomes unlikely that prophylactic intervention has a profound impact on mortality. On the other hand, the

choice of outcome in prevention of gastrointestinal bleeding would be much more appropriate, much more sensitive to the proposed intervention.

Can this GIB reduction outcome be considered relevant? Yes, it is a relevant outcome because it can lead to new interventions such as endoscopy, blood transfusion, and longer hospitalization. These new interventions for GIB treatment may, in turn, lead to an increase in hospitalization costs. It is important to stress that all this analysis was done based on the secondary outcome. It should be noted that the NNT is calculated by the Absolute Risk Reduction, which is related to the risk of each patient. This means that patients with low risk of SGI, without the severity found in this trial, would have a much less evident benefit in the implementation of this prophylaxis. This conclusion is reinforced by the subgroup analysis of patients with SAPS III above 53, tending to benefit, when compared to patients with SAP III below this value. Thus, this is a hypothesis that should be adequately tested in a well-designed, randomized, placebo-controlled, double-blinded, multi-center trial whose primary outcome would be GI bleeding.

Does this study have the potential to be a bedside behavior modifier? It depends on the prism of the question. If the question is about mortality, the answer is "YES," we should abandon the indiscriminate use of PPI in ICUs. But probably the most appropriate question would be about reducing SGI. In this case the answer would be "NO". In patients at high risk of gastrointestinal bleeding, the use of PPIs may prevent bleeding events without increasing related adverse events. In strata of patients of lower severity, however, this potential benefit is even more questionable, since the risk of GIB is reduced.

Conclusion

Dr. Santos Biondi reports personal fees and non-financial support from Werfen - Rotem, outside the submitted work, in the form of paid lectures and advisory board membership. No other financial, legal or political competing interests with third parties (government, commercial, private foundation, etc.) were disclosed for any aspect of the submitted work.

Competing interests

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