December 2, 2014

Dear Editor,

Please find enclosed the edited manuscript in Word format (file name: 14719-review.doc).

Title: Proton-pump inhibitors for prevention of upper gastrointestinal bleeding in patients with end-stage renal disease: a retrospective cohort study

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We greatly appreciate the opportunity to revise our paper in light of reviewers' comments and resubmit it for publication on *World Journal of Gastroenterology*. We made our best efforts in order to make the requested revisions in light of the editor and reviewer's comments. Below you can find an itemized, point-by-point detailed response to all the questions and comments of the reviewers. We hope our paper is now suitable for publication on *World Journal of Gastroenterology* in its present form and we are now resubmitting it to your attention.

The manuscript has been improved according to the suggestions of reviewers:

Reviewer 00494239
We appreciate the reviewer's thoughtful comments

Comments:
The low-dose PPI was not clearly defined (dosage ? frequency ? duration?) and the policy of medical insurance coverage of low-dose PPI was also not clearly described (for previous GI bleeding? for dyspepsia? for Hp eradication?) in this study

Reply:
We added dosage, frequency and duration of PPIs (152 patients with pantoprazole 20mg once daily and 23 with rabeprazole 10mg once daily after the initiation of dialysis) and PPIs were prescribed for epigastric soreness, dyspepsia, reflux symptom or prevention of GI complication in patients with anti-platelet drugs or warfarin.

Comments
The most important risk factor for UGIB, Helicobacter pylori, is not analyzed in the study.

Reply:
We excluded patients with a past history of peptic ulcer (gastric and/or duodenal), and among study patients, only 76 patients underwent endoscopy before initiation of dialysis. Twenty-one patients of 76 were infected with H. pylori. As your comments, we examined H pylori in only a small portion of patients and described our limitation in the discussion session. We also think that prospective controlled study is necessary to confirm our retrospective results.

Comments

The wide 95% CI of hazard ratio of PPI for UGI bleeding was noted. A very wide interval (1.84-101.64) may indicate that more data should be collected before anything very definite can be said about the parameter.

Reply:

We performed power analysis for multiple regression analysis and statistical power was 0.999 (N=544, number of predictors =11, R^2 = 0.1, probability level = 0.05). We think that wide range of 95% CI is associated with low occurrence of UGI bleeding events in the control group and too many predictors in multivariate analysis.

Comments

Although this retrospective study excludes patients who had previous peptic ulcers, but it is still difficult to make sure those enrolled patients had no peptic ulcers. The percentage of peptic ulcer between groups also had influence on clinical result.

Reply:

We accepted your comments because a small portion of patients were underwent endoscopy before initiation of dialysis. However, patients undergoing dialysis are increasingly elderly and have more co-morbidity. Before the initiation of dialysis, performing endoscopy in all patients is difficult and not evident if they had not symptoms. The incidence of UGI bleeding in the control is similar with the incidence of UGI bleeding in USRDS data and the incidence of UGI bleeding in the PPI group is relatively very low considering that they are dialysis patients, although there was no patient with peptic ulcer at the initiation of dialysis. As your comments, our retrospective data can't confirm the preventive effect of PPIs for prevention of UGI bleeding but can suggest its protective effects in patients with ESRD.

Comments

As shown in Table 1, less than 5% ESRD patients used anticoagulation. It is hard to believe this. I guessed that the word should be changed to "coumadin".

Reply

Anticoagulation means taking warfarin. We changed anticoagulation to warfarin as you commented at Table 1 and Table 3.

Comments

Page 8, it's wrong to describe "Univariate analysis showed that coronary artery disease, PPIs use, anti-coagulation and anti-platelet therapy were associated with UGIB." It should be "no use of PPIs" rather than "PPIs use".

Reply

We changed to no use of PPIs.

Reviewer #01427092

We appreciate the reviewer's thoughtful comments

Comments

The manuscript entitled "Proton-pump inhibitors for prevention of upper gastrointestinal bleeding in patients undergoing dialysis" was reviewed. This retrospective study was interesting,

but limitations were exist. Endopoints of this study was inappropriate. All-cause mortality should be adopted.

Reply

Although ESRD patients with UGI bleeding have higher risk of all-cause mortality, UGI bleeding is not leading cause of death in dialysis patients. However, UGI bleeding is important morbidities in patients with ESRD. In our cohort, there was one death related to UGI bleeding during the study period.

After medical coverage of low dose PPI in patients with GI symptoms, the use of PPI was increasing. However many clinicians have doubts about the preventive effect and safety of PPIs in dialysis patients. Our result showed that the use of PPIS was associated with a significant reduction in UGI bleeding events and there was no significant difference in mortality according to the use of PPI. We concluded that the use of PPIs was beneficial in reducing UGI bleeding and may be safe in patients with ESRD.

Reviewer #0282818

We appreciate the reviewer's thoughtful comments

Comments

Well-done retrospective study--I was surprised that no bleeding from angiodysplasia was noted. Do you really mean that PPI therapy was associated with INCREASED risk of UGI bleeding? If so, how do you account for that given the dramatic reduction in risk in multivariate analysis?

Reply

Due to the retrospective nature of this study, we cannot investigate the mechanism of preventive effect of PPI exactly. Because the preventive effect of PPI is well-known for mucosal injury in patients taking NSAIDs or anti-platelet therapy, considering most of our study patients were taking antiplatelet drug, we think that could show the dramatic reduction of bleeding events. Although we cannot exactly rule out that angiodysplasia could exist our study patient before dialysis, our endoscopic findings cannot find angiodysplasia. Our study showed that gastric and/or duodenal ulcers were the most common cause of UGI bleeding, accounting for 65.9 %.

Thank you again for publishing our manuscript in the *World Journal of Gastroenterology*.

Sincerely yours,

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