April 3th, 2014.

Dear Editor,

Please find enclosed the edited manuscript in Word format (file name: 7922-review.doc).

Title: Efficacy and Safety of Endoscopic Prophylactic Treatment with Undiluted Cyanoacrylate for Gastric Varices

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The manuscript has been improved according to the suggestions of reviewers:
1 We have clarified that this is a brief article.

2 We have provided language certificate by professional English language editing company.

3 We have added the comments to the text with: background, research frontiers, related publications, innovations and breakthroughs, applications, terminology and peer review.

4 Revision has been made according to the suggestions of the reviewer:

Reviewer # 1 (02570184)
Dear Authors, I enjoyed reading the article and congratulate you for wonderful results. I have got one suggestion, please continue the study in order to have at least 50 patients and please make the study comparative (e.g. with Histoacryl).

Answer - We thank you for reviewing our study. We are actually planning a prospective study comparing both drugs in these patients.

Reviewer # 2 (00505502)

It is interesting that this study was the first to determine the efficacy and safety of prophylactic treatment by undiluted N-butyl-2 cyanoacrylate plus methacryloxysulfolane (NBCM) for gastric varices. And the authors concluded endoscopic injection with NBCM, without lipiodol, may be a safe and effective treatment for primary prophylaxis of gastric varices bleeding. But, they need some major revisions as follow. The patients had relatively good liver function, almost all were classified Child A (65%). There is a possibility of selection bias. Please discuss about this matter. As authors described, this is a single arm study and included small number of patients. To conclude the efficacy and safety, they need to compare to conventional treatment options, if possible retrospectively compare to N-butyl-2 cyanoacrylate diluted with lipiodol. Four patients (20%) of 20 patients were failed in follow up, despite the small number of patients in this study. To conclude the long-term efficacy (recurrence or bleeding) of NBCM, authors need more patients. Minor points Abstract: Authors described that

endoscopy was performed at 3 months, 6 months and 6 and 12 months. Is this a mistake? Our study has some limitations. The number of patients was small and the method was not compared with other therapeutic options. Please describe the details of characteristics (Child-class, endoscopic findings, etc.) in two recurrent cases Please describe the details of minor adverse events in Table 3. How is the economical merit in NBCM (Glubran 2?) compared with conventional method (N-butyl-2 cyanoacrylate diluted with lipiodol).

Answer - We appreciate the suggestions. Our study has some limitations. The number of patients was small, most with good liver function (65% Child A) and this is a single arm study performed in a single institution, with no comparison to other treatment. We attributed a higher number of patients with Child-Pugh A due to the design of this study, which selected patients for primary prophylaxis of GV bleeding (we've added this sentence to the manuscript).

The results of this study using NBCM were similar to a previous study performed in our institution, which included 23 patients with gastric varices treated with cyanoacrylate diluted in lipiodol (Martins FP, Macedo EP, Paulo GA, Nakao FS, Ardengh JC, Ferrari AP. Endoscopic follow-up of cyanoacrylate obliteration of gastric varices. Arq Gastroenterol 2009; 46: 81–84). But unfortunately there are no prospective studies comparing NBCM versus cyanoacrylate diluted with lipiodol.

Because of characteristics of our population we also had a reasonable follow-up failure in 20% of our patients. All these points may represent some important bias on our study results, but to our best knowledge this is the first study to evaluate feasibility, efficacy and long-term safety of NBCM for GV bleeding prophylaxis in adults. On the other hand, there are only few studies reporting efficacy and long-term safety of prophylactic CYA injection for GV. Another important issue is cost. In Brazil NBCM is more expensive than CYA plus lipiodol injection (twice more expensive than cyanoacrylate), but a complete economical evaluation is out of our study scope, and should include not only the drug's price, but the whole cost of treatment and possible complications.

Suggestion: Minor points – Abstract: Authors described that endoscopy was performed at 3 months, 6 months and 6 and 12 months. Is this a mistake?

Answer - The reviewer is correct, and the mistake on the text was changed.

Suggestion: Please describe the details of characteristics (Child-class, endoscopic findings, etc.) in two recurrent cases.

Answer – Only 1 patient had GV recurrence at 6-month follow-up. He had hepatitis C infection, Child-Pugh A, large (F2) type 2 gastroesophageal varices with red spots. And another one had recurrence at 35-month follow-up. This patient had liver disease due to alcohol (Child-Pugh B), large (F2) type 1 gastroesophageal varices at first endoscopy evaluation. (Such details were included in the manuscript)

Suggestion: Please describe the details of minor adverse events in Table 3

Answer - The minor adverse events were only epigastric pain. Table 3 was changed.

Finally, we changed the text on the final conclusion:

In conclusion, although our findings are subject to some limitations (small series, patients with good liver function, one arm design in a single institution, and loss to follow up of some patients), our results suggest that endoscopic injection with NCBM, without lipiodol, may be a safe and effective primary prophylactic for gastric variceal bleeding.

We appreciate the suggestions and hope that our responses have been satisfactory.

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

Sincerely yours,

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