

Format for ANSWERING REVIEWERS



October 14, 2014

Dear Editor,

Please find enclosed the edited manuscript in Word format (file name: 12824-review.doc).

Title: Effect of esophageal variceal ligation and intravariceal sclerotherapy combined with esophageal mucosa sclerotherapy using small-volume sclerosant for cirrhotic patients with high variceal pressure

Author: De-Run Kong, Jin-Guang Wang, Chen Chen, Fang-Fang Yu, Qiong Wu, Jian-Ming Xu

Name of Journal: *World Journal of Gastroenterology*

ESPS Manuscript NO: 12824

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

1 Format has been updated

2 Revision has been made according to the suggestions of the reviewer

Reviewer code: 00039316

Q Small sample size and short FU period preclude any conclusion. Moreover, exclusion of Child-Pugh Class C patients, who are to be benefited more of the treatment also weakens the study. Variceal pressure measurement as performed in the study cannot replace the invasive measurement required

for a clinical trial.

Responses to Q : Thank you for your comments. The main objective of our study was to determine whether there was difference in variceal rebleeding rates between EVL and intravariceal - mucosa sclerotherapy. It has been suggested previously that a large sample size would be required to show a difference in bleeding rates if the study population was comprised of an unselected patient population with varices. To reduce the heterogeneity, we randomized only those patients with large varices ($\geq F2$) and variceal pressure ≥ 15.2 mm Hg. Despite our selection, it is possible that the small sample size may have masked the potential bleeding risks. In the revision, I will add more discussion about the limitations of our study.

Local treatments act at the variceal bleeding site, without modifying the underlying pathophysiological abnormalities leading to bleeding. The best examples are endoscopic procedures (EIS, EVL). These procedures are often effective only for a short time, since portal pressure and blood-flow remain unchanged, and varices frequently recur (about 50% at 2 years). However, our randomized controlled trial with a maximum of 2 years of follow-up is better than that of any other published study of a single intravariceal - mucosa sclerotherapy in this setting.

In previous study, it was speculated that repeated sclerotherapy sessions might be poorly tolerated by patients in Child-Pugh classes C and might have contributed to the precipitation of liver failure and other common complications of cirrhosis (Saira H, et al. Preventing a first episode of esophageal variceal hemorrhage. CLEVELAND CLINIC JOURNAL OF MEDICINE, 2008,75:235-43). TIPS is more effective than endoscopic therapy in preventing rebleeding in patients with Child-Pugh class C (a score of 10 to 13) (García-Pagán, et al. Early use of TIPS in patients with cirrhosis and variceal bleeding. NEJM, 2010,362:2370-9). In our hospital, the patients with Child-Pugh class C were going to do TIPS, so they were excluded from the study.

Not only is intravariceal pressure the best parameter for predicting rupture of varices and consequent complications, but it is also a useful guide for studying the effect of pharmacotherapy of portal hypertension and a measure of the effects of transjugular intrahepatic portosystemic shunting (Rakesh K, et al. Measuring intravariceal pressure. Endoscopy, 2009,70:414-5). Previous studies have demonstrated that the cirrhotic patients with a high risk of variceal bleeding were associated with variceal pressure ≥ 15.2 mmHg (Nevens F, et al. Variceal pressure is a factor predicting the risk of a first variceal bleeding: a prospective cohort study in cirrhotic patients. Hepatology, 1998; 27: 15-9).

Reviewer code: 02861175

Q Dear authors. I interest to your study. This study can be decreased re-bleeding risk after band ligation. The bleeding tendency in liver cirrhotic may occur not only from esophageal varic, but may be from gastric varic or portal hypertention gastropathy. Did you asses these conditions before or after treatment? advise: - take notes of statistical analyses used below the table. - change the figure with a good picture.

Responses to Q : Thank you for your advice. In our study, gastric varices and portal gastropathy in all patients also been accessed before or after treatment, but the difference was not statistically important. As you suggested, we have added required the details about gastric varices and portal gastropathy after treatments in the revision. We add a picture before treatment to show the procedure, and also add statistical analyses below the table.

Reviewer code: 02948135

Q Dear Authors, It is a pleasure to read and review your study, Obviously you put lots of efforts in it and that is reflected well. I have few points that i think would be complementary to the overall value of your research.

1. The banding group is treated every 2-3 weeks while the combined group

every 1-2 weeks, please explain why this discrepancy?

2. One of the important features of any study is avoiding or minimising the bias. It is not clear who assess the post intervention primary and secondary outcomes, I'm very much interested to show me who you have excluded or minimise the bias in this section.

3. Please explain why your combined group doing well in terms of primary and secondary outcomes? What is the pathophysiology behind? how your technique works while banding don't.

4. The study was conducted over 4 years, do you have the ethical approval in 2008 or you got it retrospectively. If it is retrospective , then there would be ethical problem as this intervention could result in major incident.

5. Some unsuitable syntax like "Patients who fulfilled the inclusion and exclusion criteria were immediately randomized to either EVL group or combined group." it should be patients who fulfilled the inclusion criteria were ...because the excluded patients were not involved in this study.

6. It is also important to know who performed the intervention and what endoscopic experience they have.

7. The authors should defend the idea that submucosal injection is not going to cause oesophageal stenosis and dysphagia

8. Authors also discuss why they choose a pressure of 15 as threshold and whether the technique can be use in other patients , at least from theoretical point of view.

Responses to Q :

1. In patients with EVL, complete reepithelialization takes place in 14-21 days, with full-thickness replacement of the vascular structures with maturing scar tissue. The most worrisome complication was bleeding due to untimely sloughing of bands caused by inadvertent contact with the endoscope during follow-up endoscopy. For this reason, we have now adopted a 2-3 weeks interval between ligation sessions (Roberto.F, et al. Endoscopic treatments for portal hypertension. SEMINARS IN LIVER DISEASE, 1999,19:439-55).

However, in patients with intravariceal - mucosa sclerotherapy, mucosal ulcerations occur in up to 90% of patients within 24 hours of injection and heals rapidly in most cases. So, we have now adopted a 1-2 weeks interval between sclerotherapy sessions.

2. To avoid or minimize the bias, we used consecutively numbered envelopes that contained the treatment assignments, which were generated by a system using computer-allocated random digit numbers. Patients randomized to EVL or sclerotherapy groups underwent band ligation or intravariceal - mucosa sclerotherapy until all esophageal varices were obliterated or were significantly reduced to small residual varices F1. In the paper, we have shown the details about dividing groups.

3. Intravariceal - mucosa combined sclerotherapy may obliterate interconnecting perforating varices and achieve decrease of variceal recurrence. Thus, combined group can be more useful in eradicating the varices completely than the banding ligation. According to the AASLD practice guidelines, patients underwent serial (every 2–3 weeks) band ligation until all esophageal varices completely disappeared or were significantly reduced to small residual varices F1 (Garcia-Tsao, et al. Prevention and management of gastroesophageal varices and variceal hemorrhage in cirrhosis. *HEPATOLOGY*, 46, 2007:923-38).

4. The protocol was approved by the Ethics Committee in Anhui Medical University (Current Controlled Trials number: Clinical Trial Registry -TRC-08000252), which was mentioned in the paper.

5. Thank you very much for your remind. Your suggestions help us greatly in improving the manuscript. In the revision, we will revise the unsuitable sentences.

6. This was a single-center study, with all endoscopic treatments performed by a single physician (DR.K) of 26 years endoscopic experience. In the revision, we will add the details.

7. In the revision, we will present the idea that submucosal injection will

induce submucosal fibrosis and obliteration of deeper perforating vessels, but not going to cause oesophageal stenosis and dysphagia.

8. Previous studies have demonstrated that the cirrhotic patients with a high risk of variceal bleeding were associated with variceal pressure ≥ 15.2 mmHg (Nevens F, et al. Variceal pressure is a factor predicting the risk of a first variceal bleeding: a prospective cohort study in cirrhotic patients, *Hepatology*, 1998; 27: 15-9). However, the technique can be use in all cirrhotic patients with portal hypertension and esophageal varices, especial in patients with high bleeding risk, such as the variceal pressure ≥ 15.2 mmHg.

3 References and typesetting were corrected

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

Sincerely yours,

De-Run Kong, MD

1st Affiliated Hospital

Anhui Medical University

Hefei, 230022

PR China

Fax: +86-551-5120742

E-mail: kdr168@sohu.com