

Carvedilol as an adjunct to endoscopic cyanoacrylate injection for secondary prophylaxis of gastric variceal bleeding

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Principle investigator: Wen-Chi Chen, MD

Division of Gastroenterology and Hepatology, Department of Internal Medicine,

Kaohsiung Veterans General Hospital,

No. 386, Ta-Chung 1st. Rd., Kaohsiung City 813, Taiwan

Tel: +886-7-3422121 ext. 2075; Fax: 886-7-3468237; Email: wcchen@vghks.gov.tw

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Materials and methods

Patients

Cirrhotic patients presenting with acute GVB were evaluated for eligibility.

The inclusion criteria were:

- (1) age of 20 to 80 years;
- (2) cirrhotic patients with acute GVB proven by endoscopy within 24 h of bleeding;
- (3) stable hemodynamic condition for at least 3 days after a cyanoacrylate injection.

The exclusion criteria were:

- (1) previous treatment for gastric varices (GV), including endoscopic therapy, transjugular intrahepatic porto-systemic shunt (TIPSS), or shunt surgery;
- (2) contraindications to NSBBs or cyanoacrylate injection;
- (3) serum total bilirubin > 10 mg/dL;
- (4) grade III/IV hepatic encephalopathy;
- (5) hepatorenal syndrome;
- (6) severe heart failure (NYHA Fc III/IV);
- (7) chronic kidney disease under renal replacement therapy;
- (8) refractory ascites;
- (9) malignancy other than hepatocellular carcinoma;
- (10) pregnancy;

(11) the use of a pacemaker;

(12) refusal to participate.

Randomization was performed when the hemodynamic conditions were stable, usually 3 to 5 days after initial GVO for acute bleeding. A computer-generated randomization sequence in a 1:1 ratio was used for randomization. The randomization sequences were concealed until after the patients had given consent to participate in the study and the interventions had been assigned.

The patients randomized to group A underwent repeated GVO until the varices were completely obturated. The patients randomized to group B received carvedilol in addition to repeated GVO.

General management

Patients were resuscitated with red cells and crystalloid solution. Terlipressin 1 g q6h for 3 days was immediately started on arrival at the emergency room. Prophylactic antibiotics were administered for 5 days and were adjusted according to sensitivity tests in the patients proven to have an infection. After GVO, esomeprazole 40 mg intravenous infusion twice daily was administered for 2 days, and then shifted to oral esomeprazole 40 mg daily until the ulcers associated with GVO had completely healed.

Endoscopic therapy

The patients underwent emergency GVO whenever possible, usually 4 to 12 hours after presentation. GVO was performed using an XQ-260 or H-260 endoscope (Olympus Optical Co. Ltd., Tokyo, Japan) and a 22-gauge disposable injection needle (EIS 01943, Top Co., Tokyo, Japan) with a mixture of N-butyl-2-cyanoacrylate (Histoacryl blue, Braun, Melsungen, Germany) and lipiodol (Guerbet Laboratory, Aulnay-Sous-Bris, France) in a 1:1 ratio. The maximum amount of N-butyl-2-cyanoacrylate injected was usually 2 mL per session. GVO was performed at 3- to 4-week intervals during follow-up endoscopy, with the aim of eradicating the GV. GV was considered to be complete obturated when a firm consistency of the injected GV was noted in probing with the tip of the injection needle. The patients then underwent endoscopic ultrasonography to evaluate the status of obturation if scar tissue could not be differentiated from patent GV as previously described.¹ The total amount of N-butyl-2-cyanoacrylate and the number of treatment sessions required to obliterate the GV were recorded. The patients underwent follow-up endoscopy at 6-month intervals after obturation of GV. GVO was performed if recurrent GVB was encountered or GV recurred. Banding ligation was performed using Saeed[®] multi-band ligators (Cook Medical, Bloomington, IN) or Speedband Superview Super 7[™] multiple band ligators (Boston Scientific, Marlborough, MA) for primary or secondary prophylaxis of EVB in patients with high-risk EV if they agreed.

Carvedilol administration

Carvedilol was started immediately after randomization in the patients assigned to group B at a dose of 6.25 mg daily. Patients underwent dose escalation every 3 days during the admission or every 7 days in the out-patient clinics until the maximum tolerated dose was achieved or up to 25 mg daily, with the goal of reducing the resting pulse rate by 25% but not less than 55 bpm while the systolic blood pressure was greater than 90 mm Hg. Adherence to the regimen was carefully assessed at each follow-up visit by questioning the patient and his or her relatives and counting the tablets where possible.

Management of rebleeding

The patients with recurrent GVB underwent emergency GVO. Emergency banding ligation was performed in the patients with EVB. The patients with uncontrolled variceal bleeding underwent TIPSS unless otherwise contraindicated.

Study end-points

The primary end-point of this trial was the occurrence of recurrent GVB. The secondary end-points were recurrent upper gastrointestinal bleeding, mortality or liver transplantation, and adverse events associated with both therapies.

Statistical analysis

The proposed sample size was 60 cases in each group.

Demographic data were compared between both groups. Categorical data were compared using the chi-square test or Fisher's exact test as appropriate. Continuous variables with normal distribution were compared using independent Student's t-tests, and continuous variables without normal distribution were compared using the Mann-Whitney U test. Kaplan-Meier analysis was conducted to examine the time from enrollment to the recurrence of GVB, UGIB, and mortality. A log-rank test was used to examine variations between groups. Univariate and multi-variate analyses using Cox's proportional hazards model were used to examine the risk factors associated with recurrent GVB, UGIB, and mortality. Significance was defined as $p < 0.05$ for all two-tailed tests.

References

1. Ryan BM, Stockbrugger RW, Ryan JM. A pathophysiologic, gastroenterologic, and radiologic approach to the management of gastric varices. *Gastroenterology* 2004;126:1175-89.
2. Rios Castellanos E, Seron P, Gisbert JP, et al. Endoscopic injection of cyanoacrylate glue versus other endoscopic procedures for acute bleeding gastric varices in people with portal hypertension. *Cochrane Database Syst Rev* 2015;5:CD010180.
3. Sarin SK, Lahoti D, Saxena SP, et al. Prevalence, classification and natural history of gastric varices: a long-term follow-up study in 568 portal hypertension patients. *Hepatology* 1992;16:1343-9.
4. Tan PC, Hou MC, Lin HC, et al. A randomized trial of endoscopic treatment of acute gastric variceal hemorrhage: N-butyl-2-cyanoacrylate injection versus band ligation. *Hepatology* 2006;43:690-7.
5. Lo GH, Lai KH, Cheng JS, et al. A prospective, randomized trial of butyl cyanoacrylate injection versus band ligation in the management of bleeding gastric varices. *Hepatology* 2001;33:1060-4.
6. Garcia-Pagan JC, Barrufet M, Cardenas A, et al. Management of gastric varices. *Clin Gastroenterol Hepatol* 2014;12:919-28 e1; quiz e51-2.

7. Gonzalez R, Zamora J, Gomez-Camarero J, et al. Meta-analysis: Combination endoscopic and drug therapy to prevent variceal rebleeding in cirrhosis. *Ann Intern Med* 2008;149:109-22.
8. Mishra SR, Chander Sharma B, Kumar A, et al. Endoscopic cyanoacrylate injection versus beta-blocker for secondary prophylaxis of gastric variceal bleed: a randomised controlled trial. *Gut* 2010;59:729-35.
9. Hung HH, Chang CJ, Hou MC, et al. Efficacy of non-selective beta-blockers as adjunct to endoscopic prophylactic treatment for gastric variceal bleeding: a randomized controlled trial. *J Hepatol* 2012;56:1025-32.
10. Banares R, Moitinho E, Matilla A, et al. Randomized comparison of long-term carvedilol and propranolol administration in the treatment of portal hypertension in cirrhosis. *Hepatology* 2002;36:1367-73.
11. Bosch J. Carvedilol for portal hypertension in patients with cirrhosis. *Hepatology* 2010;51:2214-8.
12. Stanley AJ, Dickson S, Hayes PC, et al. Multicentre randomised controlled study comparing carvedilol with variceal band ligation in the prevention of variceal rebleeding. *J Hepatol* 2014;61:1014-9.
13. Reiberger T, Ulbrich G, Ferlitsch A, et al. Carvedilol for primary prophylaxis of variceal bleeding in cirrhotic patients with haemodynamic non-response to

propranolol. Gut 2013;62:1634-41.

14. Shah HA, Azam Z, Rauf J, et al. Carvedilol vs. esophageal variceal band ligation in the primary prophylaxis of variceal hemorrhage: a multicentre randomized controlled trial. J Hepatol 2014;60:757-64.

15. Bosch J. Carvedilol for preventing recurrent variceal bleeding: waiting for convincing evidence. Hepatology 2013;57:1665-7.

16. Hashizume M, Kitano S, Yamaga H, et al. Endoscopic classification of gastric varices. Gastrointest Endosc 1990;36:276-80.

17. Beppu K, Inokuchi K, Koyanagi N, et al. Prediction of variceal hemorrhage by esophageal endoscopy. Gastrointest Endosc 1981;27:213-8.

18. Kamath PS, Wiesner RH, Malinchoc M, et al. A model to predict survival in patients with end-stage liver disease. Hepatology 2001;33:464-70.

19. de la Pena J, Brullet E, Sanchez-Hernandez E, et al. Variceal ligation plus nadolol compared with ligation for prophylaxis of variceal rebleeding: a multicenter trial. Hepatology 2005;41:572-8.

20. Lo GH, Chen WC, Wang HM, et al. Randomized, controlled trial of carvedilol versus nadolol plus isosorbide mononitrate for the prevention of variceal rebleeding. J Gastroenterol Hepatol 2012;27:1681-7.

21. Banares R, Moitinho E, Piqueras B, et al. Carvedilol, a new nonselective

beta-blocker with intrinsic anti- Alpha1-adrenergic activity, has a greater portal hypotensive effect than propranolol in patients with cirrhosis. *Hepatology* 1999;30:79-83.

22. Bosch J. Carvedilol: the beta-blocker of choice for portal hypertension? *Gut* 2013;62:1529-30.

23. Watanabe K, Kimura K, Matsutani S, et al. Portal hemodynamics in patients with gastric varices. A study in 230 patients with esophageal and/or gastric varices using portal vein catheterization. *Gastroenterology* 1988;95:434-40.

24. Tripathi D, Therapondos G, Jackson E, et al. The role of the transjugular intrahepatic portosystemic stent shunt (TIPSS) in the management of bleeding gastric varices: clinical and haemodynamic correlations. *Gut* 2002;51:270-4.

25. Mishra SR, Sharma BC, Kumar A, et al. Primary prophylaxis of gastric variceal bleeding comparing cyanoacrylate injection and beta-blockers: a randomized controlled trial. *J Hepatol* 2011;54:1161-7.