Research Article

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Efficacy of non-selective β-blockers as adjunct to endoscopic prophylactic treatment for gastric variceal bleeding: A randomized controlled trial

Hung-Hsu Hung[1,2,3], Chen-Jung Chang[1,2,4], Ming-Chih Hou[1,2,3,*], Wei-Chih Liao[1,2,5], Che-Chang Chan[1,2], Hui-Chun Huang[1,2], Han-Chieh Lin[1,2], Fa-Yauh Lee[1,2], Shou-Dong Lee[1,6,7]

[1]*Department of Medicine, School of Medicine, National Yang-Ming University, Taipei, Taiwan;* [2]*Division of Gastroenterology, Department of Medicine, Taipei Veterans General Hospital, Taipei, Taiwan;* [3]*Endoscopy Center for Diagnosis and Treatment, Taipei Veterans General Hospital, Taipei, Taiwan;* [4]*Division of Gastroenterology and Hepatology, Department of Internal Medicine, Taipei Medical University Hospital, Taipei, Taiwan;* [5]*Division of Gastroenterology, Department of Medicine, Taipei Municipal Gan-Dau Hospital, Taipei, Taiwan;* [6]*Deparement of Medicine, School of Medicine, National Defense Medical Center, Taipei, Taiwan;* [7]*Cheng Hsin General Hospital, Taipei, Taiwan*

Background & Aims: Gastric variceal obturation (GVO) therapy is the current treatment of choice for gastric variceal bleeding (GVB). However, the efficacy of non-selective β-blockers (NSBB) in the secondary prevention of GVB is still debatable. This study aimed at evaluating the efficacy of additional NSBB to repeated GVO in the secondary prevention of GVB.

Methods: From April 2007 to March 2011, 95 patients with GVB after primary hemostasis using GVO were enrolled. Repeated GVO were performed until GV eradication. Forty-eight and 47 patients were randomized into the GVO alone group (Group A) and the GVO + NSBB group (Group B), respectively. Primary outcomes in terms of re-bleeding and overall survival were analyzed by multivariate analysis.

Results: After a mean follow-up of 18.10 months in group A, 26 patients bled and 20 died. In group B, 22 patients bled and 22 died after a mean follow-up of 20.29 months. The overall re-bleeding and survival rates analyzed by the Kaplan–Meier method were not different between the two groups ($p = 0.336$ and 0.936, respectively). The model of end-stage liver disease (MELD) score and main portal vein thrombosis (MPT) were independent determinants of re-bleeding while MPT and re-bleeding were independent factors of mortality by time-dependent Cox-regression model. Asthenia was the most common adverse event and was higher in group B ($p < 0.001$).

Conclusions: Adding NSBB therapy to repeated GVO provides no benefit for the secondary prevention of bleeding and mortality in patients with GVB.

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Keywords: Beta-blocker; Cyanoacrylate injection; Gastric variceal bleeding; Re-bleeding; Secondary prevention.

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* Corresponding author. Address: Department of Medicine, School of Medicine, National Yang-Ming University, Taipei Veterans General Hospital, No. 201, Sec. 2, Shih-Pai Rd., Taipei, Taiwan. Tel.: +886 2 2871 2121x3218; fax: +886 2 2874 5074.

E-mail address: mchou@vghtpe.gov.tw (M.-C. Hou).

Abbreviations: GV, gastric varices; EV, esophageal varices; GVB, gastric variceal bleeding; EVB, esophageal variceal bleeding; TIPS, trans-jugular intra-hepatic porto-systemic shunt; GOV, gastro-esophageal varices; IGV, isolated gastric varices; GVO, gastric variceal obturation; NSBB, non-selective β-blockers; RCT, randomized controlled trial; OPD, out-patient department; HCC, hepatocellular carcinoma; MPT, main portal vein thrombosis; PHG, portal hypertensive gastropathy; MELD, model of end-stage liver disease; EVL, esophageal variceal ligation; HR, hazard ratio; CI, confidence interval; INR, international normalized ratio; IRB, Institutional Review Board; SD, standard deviation; SPSS, Statistical Package for Social Sciences.

Introduction

Gastric varices (GVs) are less common than esophageal varices (EVs) and occur in around 20% of patients with portal hypertension [1]. Although the incidence of gastric variceal bleeding (GVB) is lower than esophageal variceal bleeding (EVB), GVB has a higher re-bleeding rate, requires more blood transfusion, and has a higher mortality rate [1–3]. The importance of preventing GV re-bleeding cannot be over-emphasized.

Secondary prevention of GVB includes gastric variceal obturation (GVO), non-selective β-blockers (NSBB), trans-jugular intrahepatic porto-systemic shunt (TIPS), surgical shunts, and liver transplant [4]. Among these therapies, GVO is shown to be very effective with a consistent success rate of 90–100% in controlling acute GVB [5–8]. However, cyanoacrylate injection is complicated and can lead to bacteremia, sepsis, embolism, and endoscopic injury [9,10].

NSBB is effective in reducing re-bleeding and death from EVs by 40% and 20%, respectively [11]. However, its efficacy as secondary prevention of GVB has limited evidence [12]. In a previous study, repeated GVO appeared to be more effective than NSBB as secondary prevention and in improving survival of GVB patients [12].

Although the recent meta-analysis and Baveno V consensus suggests a combination of endoscopic and drug therapy is more effective than either therapy alone in the secondary prevention of EV bleeding [13], the evidence is limited for the combination therapy in the secondary prevention of GV bleeding. As a whole,

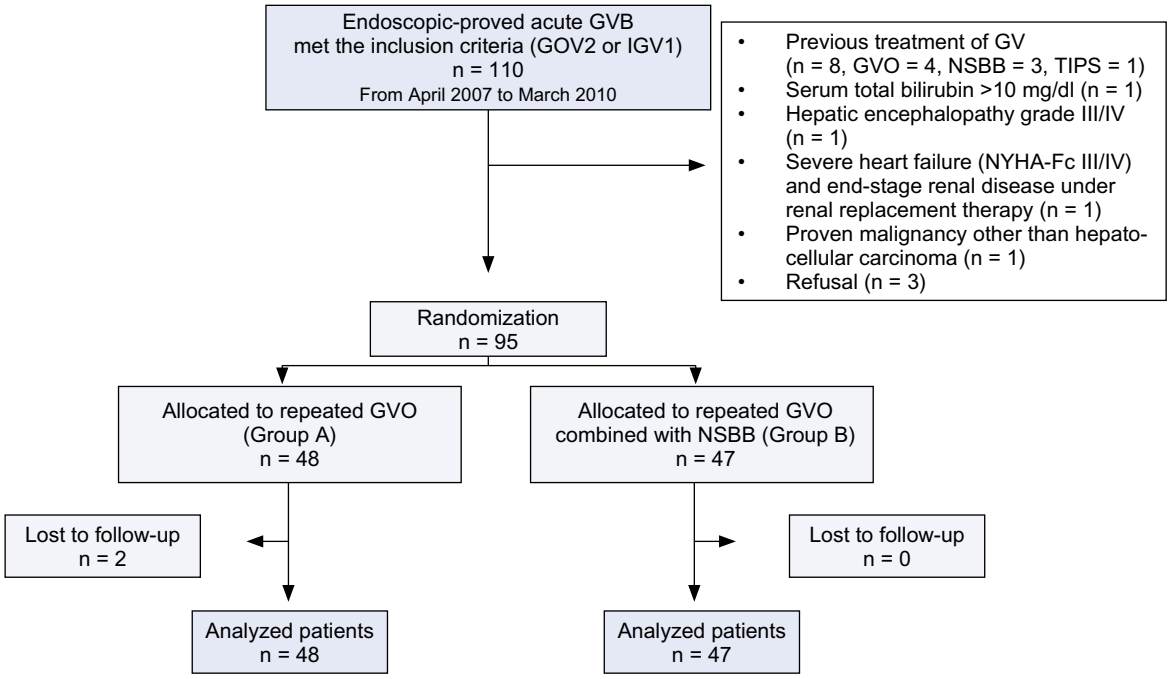

Fig. 1. The flow chart of the study.

the secondary prevention of GV bleeding remains sub-optimal in comparison to the secondary prevention of EV bleeding [12,14–16]. The current prospective randomized controlled trail (RCT) aimed at evaluating whether additional NSBB can improve re-bleeding and mortality rates in patients who undergo repeated GVO after primary hemostasis.

Materials and methods

Patients

Cirrhotic patients with acute GVB were enrolled consecutively at the Taipei Veterans General Hospital from April 2007 to March 2011 and the last randomized subject received the treatment protocol for at least 3 months. The inclusion criteria were (1) age of 18–80 years; (2) type 2 gastro-esophageal varices (GOV_2) or type 1 isolated gastric varices (IGV_1); (3) GVB proven by endoscopy and GVO within 24 h of bleeding; and (4) stable hemodynamic condition for at least 3 days after GVO.

The exclusion criteria were (1) previous treatment of GV, including endoscopic therapy, NSBB, TIPS, or surgery; (2) contraindications to NSBB or cyanoacrylate injection; (3) serum total bilirubin >10 mg/dl; (4) hepatic encephalopathy grade III/IV; (5) hepato-renal syndrome; (6) severe heart failure (NYHA Fc III/IV); (7) end-stage renal disease under renal replacement therapy; (8) severe chronic obstructive pulmonary disease; (9) proven malignancy other than hepatocellular carcinoma (HCC); (10) pregnancy; (11) pacemaker use; and (12) refusal to participate.

The contraindications of NSBB were (1) bronchial asthma; (2) chronic obstructive pulmonary disease (COPD); (3) uncontrolled heart failure; (4) sinus bradycardia <60/min; (5) heart block greater than first degree; and (6) cardiogenic shock.

The patients were randomized consecutively to two groups using numbered envelopes that contained the treatment regimens, which were generated by a system using computer-allocated random digit numbers. Randomization was performed as long as hemodynamic conditions were stable, usually 3–5 days after initial GVO for acute bleeding (Fig. 1). In group A, the patients underwent repeated endoscopic cyanoacrylate injection every 3–4 weeks until GV eradication. Patients in group B also underwent the repeated GVO protocol as group A but had additional NSBB treatment. The hospital's Institutional Review Board (IRB) approved the study and written informed consent was obtained from each patient before enrollment.

Gastric variceal obturation

Endoscopic intervention was performed by using an Olympus XQ-240 or XQ-260 endoscope (Olympus Optical Co. Ltd., Tokyo, Japan) and a 22-gauge disposable injection needle (EIS 01943, Top Co., Tokyo, Japan). Each shot contained 0.5 ml *n*-butyl-2-cyanoacrylate (Histoacryl blue, Braun, Melsungen, Germany) and 0.5 ml lipiodol (Guerbet Laboratory, Aulnay-Sous-Bris, France), with no more than six shots per session. After GVO, omeprazole 40 mg intravenous infusion twice daily was prescribed for 2 days, and then shifted to oral esomeprazole 40 mg per day for another 12 days.

Beta-blockers therapy

Propranolol was started at a dose of 10 mg twice daily as soon as hemodynamic stability was achieved after GVO. The dose was doubled every 3 days in the hospital or every 7 days in the out-patient department (OPD) if the target dose was not reached. The target dose was achieved when one of the following criteria was satisfied: (1) >25% reduction of baseline heart rate; (2) a target heart rate of approximately 55/min; and (3) a maximum dose of 320 mg per day if well tolerated and with systolic blood pressure >90 mm Hg [4,17]. Compliance was carefully assessed by interview with patients or relatives on every OPD follow-up.

Clinical assessment and follow-up

Information regarding presentation of upper gastrointestinal bleeding was carefully recorded from the patients and their relatives. Vital signs, biochemistry data, amount of blood transfusion, infection status, medication, and endoscopic findings were also recorded as detailed as possible.

If there were no symptoms or signs of bleeding, follow-up endoscopy was regularly performed every 3–4 weeks and repeated GVO was performed until the GVs were eradicated (Fig. 1). After eradication, surveillance endoscopy was performed every 3 months. If bleeding symptoms or signs were noted during follow-up, emergency endoscopy was performed to localize and treat the bleeding source as soon as possible. Vasoactive agents, proton-pump inhibitor, antibiotics, or balloon tamponade were allowed as treatment of acute upper gastrointestinal bleeding according to the bleeding focus and indications. If re-bleeding occurred, conservative treatment, endoscopic treatment, TIPS, or surgery were offered based on the preference of the patients or their families.

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