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Primary prophylaxis of variceal bleeding in cirrhotic patients: A cohort study

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Abstract

Background. Current guidelines recommend beta-blockers for primary prevention of variceal haemorrhage in cirrhotic patients, and band ligation for patients with contraindications or intolerance to beta-blockers. However, it has been suggested that these patients may respond poorly to band ligation.

Aim. We evaluated the usefulness of a strategy in which band ligation was used to treat patients with contraindications or intolerance and patients not responding to beta-blockers identified by hepatic vein pressure gradient measurement. Haemodynamic responders and patients refusing hepatic vein pressure gradient measurement were given long-term beta-blockers.

Methods. One hundred and thirty-five consecutive patients with high-risk oesophageal varices and no prior bleeding were enrolled. Twenty-five patients with contraindications (group A), 26 with intolerance to beta-blockers (group B) and 25 showing a poor haemodynamic response (Group C) underwent band ligation. Twenty-two haemodynamic responders (Group D) and 37 refusing hepatic vein pressure gradient measurement (Group E) were treated with beta-blockers.

Results. Median follow-up was 32 months. 12/135 patients (8.9%) bled: 3/25 (12%) in group A, 1/26 (3.8%) in group B, 0/25 (0%) in group C, 0/22 (0%) in group D and 8/37 (22.2%) in group E. Mortality was 8/135 (5.9%).

Conclusions. Patients with contraindications, intolerance or not responding to beta-blockers treated with band ligation achieve protection from variceal bleeding comparable to that of good responders to beta-blockers.

Keywords: Beta-blockers; Endoscopic band ligation; Hepatic vein pressure gradient; Oesophageal varices

1. Introduction

Non-selective beta-blockers are the recommended first-line therapy for the primary prophylaxis of variceal haemorrhage in cirrhotic patients with varices at high risk for bleeding [1]. Beta-blockers reduce the 2-year incidence of first bleeding in these patients by 40% [2]. However, beta-blockers are not suitable for all patients: contraindications may be present in 5–20% of potential candidates [3], and 9–33% may develop side effects that lead to discontinuation of the treatment in 3–27% of cases [3,4]. Protection from bleeding under beta-blocker treatment is related to the extent of portal pressure reduction as measured by the hepatic vein pressure gradient (HVPG): patients are totally protected from bleeding when the HVPG is reduced to $\leq$12 mmHg, and achieve a good degree of protection when the HVPG,

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although still above 12 mmHg, is decreased by ≥20% from baseline [5]. Patients not reaching these haemodynamic targets are less protected from bleeding. Unfortunately, a HVPG reduction to ≤12 mmHg or by 20% is achieved in a minority of patients (27–36% in different studies [5–7]). Therefore, three different patient populations exist in which beta-blockers cannot be used or are ineffective: those with contraindications, those with intolerance and those who do not adequately respond haemodynamically. The optimal strategy to manage these patients is not defined yet: the current recommendation is to treat with band ligation (EBL) the patients with contraindications or intolerance to beta-blockers [8]; however, it has been recently suggested that these patients may respond poorly to EBL [9]. Although there is a consensus that the usefulness of HVPG measurement in primary prophylaxis deserves further study [8,10], HVPG measurement is not considered mandatory in this setting [10], because the risk of bleeding in these patients is deemed too low to warrant the effort. Nevertheless, it is disturbing to know that more than 50% of patients treated with beta-blockers receive an unnecessary treatment.

Aim of this study was to evaluate whether EBL is effective in preventing the first variceal haemorrhage in patients with contraindications, intolerance or not responding to beta-blockers. We thus conducted a study in consecutive patients with liver cirrhosis and high-risk oesophageal varices, in which patients with contraindications and intolerance were treated with EBL, and in which HVPG was used to identify haemodynamic non-responders, who were treated with EBL in association to beta-blockers.

2. Patients and methods

2.1. Study cohort

Consecutive patients with cirrhosis and high-risk oesophageal varices referred to our Unit for primary prophylaxis of variceal bleeding between January 1995 and November 2006 entered the study. Inclusion criteria were: (a) cirrhosis diagnosed by histology or unequivocal clinical, laboratory and ultrasound findings, (b) high-risk varices (i.e. large oesophageal varices with or without red colour sign, or small varices with red colour sign [11,12]) diagnosed by endoscopy within the previous 2 months, (c) absence of prior variceal bleeding, (d) written informed consent to the procedures. Exclusion criteria were: (a) advanced hepatocellular carcinoma and (b) complete portal vein thrombosis at baseline.

One hundred and thirty-five patients entered the study.

2.2. Study design

The study algorithm is shown in Fig. 1. All patients were initially evaluated for contraindications to beta-blockers: those with contraindications (asthma, chronic obstructive lung disease, sinus brady-arrhythmia, second and third-degree atrioventricular block and decompensated insulin-dependent diabetes mellitus) underwent EBL. Those without contraindications were offered HVPG measurement. Patients who refused the latter were given beta-blockers, and if they developed intolerance (symptomatic hypotension, severe bradycardia, severe fatigue, encephalopathy, loss of libido) were shifted to EBL. The remaining patients underwent HVPG measurement and were given beta-blockers. Again, those who developed intolerance to beta-blockers at this stage underwent EBL. After stabilization of beta-blocker treatment, tolerant patients were offered a second HVPG measurement. Those who refused were continued on beta-blockers, while the remaining had a second measurement. Haemodynamic responders (showing a HVPG decrease to ≤12 mmHg or by ≥20% from baseline) continued on beta-blockers, whereas non-responders underwent EBL, while continuing beta-blockers. Thus, five groups were enrolled in the study: group A (patients with contraindications to beta-blockers), group B (patients intolerant to beta-blockers), group C (haemodynamic non-responders), group D (haemodynamic responders) and group E (patients who tolerated beta-blockers but either refused HVPG measurement altogether or refused the second HVPG measurement). Groups A and B were treated with prophylactic EBL, patients in group C received EBL plus beta-blockers, while groups D and E were treated with non-selective beta-blockers.

2.3. HVPG measurement

HVPG was measured in the supine position, via the femoral access under local anaesthesia and light sedation with diazepam 2.5 mg per os. Occlusion balloon catheters (Boston Scientific Medi-Tech, Natick, MA) were used. The HVPG value, expressed in mmHg and computed as a mean of three valid measurements, was calculated as the difference between the wedged hepatic venous pressure (WHVP) and the free hepatic venous pressure (FHVP).

2.4. Beta-blockers therapy

Patients were started on oral propranolol, 20 mg twice daily—or oral nadolol, 40 mg daily (according to the preference of the physician who had the patient in charge). The dose was increased stepwise at weekly intervals until the heart rate had fallen by 25% (or below 55 beats/min), or systolic blood pressure was below 90 mmHg, or severe fatigue developed. Mean propranolol and nadolol doses in each group are reported in Table 1; the overall mean daily doses were 50.2 ± 5.4 mg for propranolol and 71.0 ± 5.0 mg for nadolol.

2.5. Endoscopic EBL

Endoscopic EBL was performed in all patients within 1 month from the indication, at 2-week intervals until eradication was achieved. EBL was initially performed with the