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Nonselective β-blockers may induce development of portal vein thrombosis in cirrhosis

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Abstract

Currently, nonselective β-blockers (NSBBs) are commonly used for the prevention of variceal bleeding in liver cirrhosis. The beneficial effects of NSBBs are primarily attributed to the reduction in cardiac output by blockade of β1 receptors and vasoconstriction of the splanchnic circulation by the blockade of β2 receptors. The prognostic value of occlusive portal vein thrombosis (PVT) in cirrhotic patients has been increasingly recognized. The most important risk factor for the development of PVT in liver cirrhosis is the decreased portal vein inflow velocity. Collectively, we propose that the use of NSBBs potentially increases the development of portal vein thrombosis by reducing portal vein inflow velocity. The hypothesis should be confirmed by prospective cohort studies, in which cirrhotic patients without prior PVT treated with and without NSBBs are enrolled, and the development of PVT during follow-up is compared between the two groups. Additionally, subgroup analyses should be performed according to the dosage of NSBBs and the reduction of portal inflow velocity after use of NSBBs.

Key words: Non-selective β-blockers; Propranolol; Nadolol; Portal vein thrombosis; Liver cirrhosis

Core tip: Non-selective β-blockers can reduce portal flow velocity and induce development of portal vein thrombosis in liver cirrhosis.

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TO THE EDITOR

Benefits of non-selective β-blockers in the treatment of cirrhotic portal hypertension

Currently, benefits of non-selective β-blockers (NSBBs), such as propranolol and nadolol, are recommended as the mainstay treatment of choice for primary and secondary prevention of variceal bleeding in liver cirrhosis in different practice guidelines and consensus statements[1-3]. This recommendation primarily originates from the positive results of numerous randomized controlled trials and meta-analyses that NSBBs significantly decrease the incidence of first or recurrent variceal bleeding and improve survival in cirrhotic patients[4-9]. It appears that the benefits of NSBBs have been the "aspirin" of the hepatologists[10]. The principle mechanisms of action of NSBBs include: (1) decreasing cardiac output by blockade of β1 receptors and (2) constricting the splanchnic

circulation by the blockade of β2 receptors. These beneficial effects can reduce the portal vein inflow velocity, thereby lowering portal vein pressure[2,3]. Certainly, several inconveniences and/or inappropriateness should not be neglected. First, approximately 15% of patients may have contraindications to NSBBs[2,3]. Second, an additional 15% of patients are intolerant of NSBBs due to drug-related adverse events[2,3]. Third, only 30%-50% of patients treated with NSBBs can achieve a sufficient hemodynamic response (a reduction in hepatic venous pressure gradient ⩾ 20% from baseline level or to ⩽ 12 mmHg)[11,12]. Fourth, NSBBs may be ineffective for preventing enlargement of small varices[13].

In addition, a meta-analysis of three randomized controlled trials and three retrospective studies demonstrated that NSBBs could prevent the occurrence of spontaneous bacterial peritonitis in cirrhotic patients, regardless of hemodynamic response[14]. Further studies showed its potential mechanism, that the use of NSBBs could ameliorate gastroduodenal and intestinal permeability and reduce bacterial translocation, irrespective of the hemodynamic effect on portal hypertension[15,16].

Adverse effects of NSBBs in treatment of cirrhotic portal hypertension

Recently, a single-center, observational, case-only, prospective study by Sersté *et al*[17] demonstrated that NSBBs were significantly associated with poor survival in cirrhotic patients with refractory ascites (median survival time: 20 mo in patients without propranolol *vs* 5 mo in those with propranolol, $P = 0.0001$). Subsequently, a self-controlled crossover study by the same investigators found that the negative prognostic effect of NSBBs might be attributed to a high risk of paracentesis-induced circulatory dysfunction in cirrhotic patients with refractory ascites[18]. The milestone study strongly suggests that the use of NSBBs should be undertaken with caution in these patients. Certainly, not all studies have supported this finding. More recently, a retrospective cohort of 114 consecutive patients undergoing regular paracentesis with or without NSBBs at modest doses (36 patients *vs* 78 patients) was analyzed[19]. Median survival time was similar between the NSBB and no NSBB groups (18 mo *vs* 11 mo, $P = 0.98$, log-rank test). In addition, Galbois and colleagues showed no effect of NSBBs on the mortality of cirrhotic patients admitted to the intensive care unit due to severe sepsis or septic shock[20]. Due to many controversies among studies, the negative effect of NSBBs on cirrhotic patients deserves further exploration.

Clinical significance of portal vein thrombosis in liver cirrhosis

Accumulated evidence has confirmed that the presence of occlusive portal vein thrombosis (PVT) is negatively associated with the outcome of cirrhotic patients, by elevating the incidence of variceal bleeding and decreasing survival[21-23]. Although the resolution of partial PVT can be frequently observed[24], the role of occlusive PVT as a clinical predictor of decompensated liver cirrhosis has been hypothesized[25]. To prevent further these detrimental effects, clinicians should pay more attention to identify cirrhotic patients at high risk of the development of PVT[26].

Risk factors of PVT in liver cirrhosis

To date, several risk factors of PVT in liver cirrhosis have been established[26-28]. The most important risk factor is decreased portal inflow velocity in liver cirrhosis. In an Italian prospective observational study by Zocco *et al*[29], a total of 100 consecutive cirrhotic patients without prior PVT were followed to evaluate whether or not *de novo* PVT developed within 1 year. Demographic, clinical, biochemical, and ultrasound imaging data at baseline were compared between patients who developed *de novo* PVT and those who did not. In univariate analysis, higher Model for End-stage Liver Disease score, lower platelet count, reduced antithrombin and protein C and S levels, and decreased portal inflow velocity < 15 cm/s were associated with the development of PVT in liver cirrhosis. In multivariate analysis, the decreased portal inflow velocity was the only independent predictor of PVT. Notably, the role of inherited coagulation abnormalities (*i.e.*, factor V Leiden and prothrombin gene mutation), which might be associated with the presence of PVT in liver cirrhosis[30,31], was not analyzed in this study. More recently, another study has confirmed the relationship between reduced portal inflow velocity and the development of PVT (mean velocity portal vein flow: 9 ± 0.9 cm/s in patients who developed *de novo* PVT *vs* 12.5 ± 2.3 cm/s in those who did not, $P < 0.001$)[32].

Possible relationship between use of NSBBs and occurrence of PVT in liver cirrhosis

Considering the capability of NSBBs to reduce portal vein inflow and portal pressure, we propose that NSBBs may further induce the occurrence of PVT in liver cirrhosis. Many uncertainties exist regarding whether or not the dosage of NSBBs and the level of portal pressure or heart rate reduction by NSBBs are associated with the occurrence of PVT. Furthermore, if possible, the clinical significance of PVT induced by NSBBs on patients' survival remains uncertain.

Ideally, this hypothesis should be confirmed by prospective cohort studies, in which cirrhotic patients without prior PVT treated with and without NSBBs are followed up, and the development of PVT is evaluated. Additionally, subgroup analyses may be necessary according to the dose of NSBBs and the reduction of portal inflow velocity after NSBB treatment.

To the best of our knowledge, the relationship between NSBBs and development of PVT in liver cirrhosis has been explored in only one European Association for the Study of the Liver abstract[32], in which 56 consecutive cirrhotic patients without hepatocellular carcinoma were enrolled and evaluated about the occurrence of PVT every 6 mo during follow-up. Multivariate analysis

demonstrated that use of NSBBs was an independent predictor of developing PVT in liver cirrhosis (OR = 3.3, 95%CI: 1.4-6.8, $P < 0.001$). These results should be further validated in well-designed prospective studies with a larger sample.

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