Editorial

Carvedilol delays the progression of small oesophageal varices in patients with cirrhosis: an unmet need finally met?

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Non-selective beta blocker (NSBB) therapy remains the front runner in the treatment of portal hypertension. Over the years, our understanding of their mechanisms of action, both haemodynamic and non-haemodynamic, has evolved. Variceal bleeding, an inevitable consequence of portal hypertension, accounts for 10% of all admissions with gastrointestinal bleeding, and has an inpatient mortality of 15% and 1 year mortality of up to 40% (1). Reducing the risk of the development of varices (pre-primary prophylaxis) and the first variceal bleed (primary prevention) are therefore important clinical goals.

NSBBs used in clinical practice are propranolol, nadolol and carvedilol. They act to reduce portal hypertension through β1 blockade and lowering cardiac output and β2 blockade leading to splanchnic vasoconstriction through unopposed α1 action (2). This results in reduced splanchnic inflow and portal pressure. Carvedilol additionally acts as a vasodilator due to its α1 receptor blockade effect which reduces porto-collateral resistance. Its actions on hepatic stellate cells lead to a reduction in intrahepatic resistance (3). Haemodynamic studies have demonstrated a greater reduction in portal pressure than propranolol, and carvedilol can be effective in non-responders to propranolol (4,5), particularly in "early" portal hypertension.

There is emerging data showing that prior to the development of clinically significant portal hypertension (CSPH) defined as hepatic venous pressure gradient (HVPG) >10 mmHg, the effect of NSBBs on reduction of portal pressure is negligible (6). The hypothesis is that at lower portal pressures, increased intrahepatic resistance rather than splanchnic vasodilatation accounts for portal hypertension. Intrahepatic resistance is not amenable to most NSBBs apart from carvedilol.

Current guidelines recommend NSBBs in reducing the risk of the first variceal bleed (primary prophylaxis) in patients with medium to large oesophageal varices or small varices and advanced liver disease or wale marks (7,8). However, paucity of evidence discourages the use of NSBBs in patients without varices (pre-primary prophylaxis), those with small varices and compensated cirrhosis or small varices in the absence of wale marks.

There are four randomised placebo controlled trials studying the role of NSBBs in patients with small varices. Cales *et al.* demonstrated that propranolol in patients with small or no varices resulted in greater development of varices (9). However, patients without varices were included and there was significant loss of patients to follow up. The second trial showed that nadolol reduced variceal bleeding in patients with small varices by 45% without survival benefit but with increased adverse events (10). Sarin *et al.* did not show any effect of propranolol in patients with small varices, despite a significant effect on portal pressure (11).

Bhardwaj *et al.* and colleagues in their well-designed randomised placebo controlled trial have shown that although carvedilol at a dose of 12.5 mg per day reduced the progression of varices over a minimum of 24 months' follow-up. There was no significant reduction in the HVPG, nor a difference in bleeding or survival in their patient cohort (12). Alcohol aetiology accounted for 21% of the treatment group. The inclusion of patients with advanced cirrhosis and ascites was a potential limitation of their study and ideally they should have only recruited

patients with compensated cirrhosis. Furthermore their findings cannot be extrapolated to a population with predominant alcohol related liver disease. Nevertheless, the promising results of carvedilol in the prevention and progression of varices have been supported by an updated meta-analysis restricted to RCTs of patients with small varices. This showed a strong trend towards reduced progression of varices with NSBBs (13).

A clear clinical effect of carvedilol in the Bhardwaj study in the absence of a reduction in portal pressure is intriguing. Studies have also shown beneficial effects of NSBBs independent of the effects on portal pressure in reducing bacterial translocation (14). Carvedilol by virtue of its anti-inflammatory, anti-oxidant, and anti-fibrotic properties as well as its role in enhancing insulin sensitivity and improving mitochondrial function appears to be a more potent NSBB than propranolol. It seems an ideal drug to study in this setting of prevention of complications of cirrhosis and portal hypertension (3).

There is a pressing need for large multicentre controlled trials recruiting patients with compensated cirrhosis that are at highest risk of development of high risk varices or decompensation. There is some evidence from an abstract which showed that NSBBs in patients (n=201) with CSPH reduced decompensation or liver related deaths but did not influence decompensation free survival (15). To see the crucial effect on clinical outcomes, such trials need to be adequately powered. Only patients with HVPG measurements >10 mmHg, i.e., CSPH ought to be selected. Ideally HVPG measuring facilities would be desirable but these are not available in many centres. The use of transient elastography (TE) and platelets count as non-invasive markers of HVPG would seem attractive. Recent studies have shown that liver stiffness measured through TE (which correlates with liver fibrosis) in combination with platelet count and spleen size is strong predictors of development of CSPH or varices requiring treatment (16-18). Liver stiffness has also been shown to predict development of other complications of cirrhosis such as ascites and hepatic encephalopathy. Another recent study evaluating the use of non-contrast quantitative magnetic resonance imaging (MRI) as a surrogate measure of portal pressure, has demonstrated that MRI parameters related to both hepatic architecture and splanchnic haemodynamics correlated significantly with HVPG (19). The future may see non-invasive markers of HVPG such as TE and MRI replacing invasive modes of HVPG measurement.

To date clinical trials of patients with small varices have not conclusively shown a reduction in bleeding or mortality, and this may reflect the small size of these trials and lack of power in these studies. However the findings by Bhardwaj and colleagues of carvedilol reducing the progression of varices should encourage further study (12). We feel that any future studies must recruit patients with evidence of CSPH i.e., HVPG >10 mmHg and/or liver stiffness/platelet count/spleen size criteria. The key is patient stratification and large scale multicentre involvement.

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