BETA-BLOCKERS IN PREVENTION OF DEVELOPMENT OF VARICES AND VARICEAL BLEEDING IN CIRRHOSIS: CURRENT MANAGEMENT, CONTROVERSIES, AND FUTURE DIRECTIONS

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One of the major complications of cirrhosis is the development of portal hypertension and variceal bleeding. Varices develop at a rate of 5% per year with a 10-year cumulative incidence of 44%.[1] Variceal bleeding accounts for 10% of all admissions with gastrointestinal bleeding; it has an inpatient mortality of 15% and a 1-year mortality of ≥40%.[2] Therefore, reducing the risk of the development of varices (pre-primary prophylaxis) and the first variceal bleed (primary prevention) are important clinical goals.

Non-selective beta-blockers (NSBBs) have been used to reduce portal pressure and variceal bleeding for >35 years. There are several key mechanisms in the pathophysiology of portal hypertension in cirrhosis, namely increased intrahepatic resistance, splanchnic vasodilation, and augmented blood flow, that result in the hyperdynamic circulation.[3] NSBBs act to reduce portal hypertension through β1 blockade, lowering cardiac output, and β2 blockade, which results in splanchnic vasoconstriction through unopposed alpha-1 action.[4] Thus, there is a reduction in splanchnic inflow and portal pressure. NSBBs used in clinical practice are propranolol, nadolol, and carvedilol. Carvedilol has additional actions as a vasodilator due to alpha-1 receptor blockade, which reduces portocollateral resistance, and by acting on hepatic stellate cells, leading to a reduction in intrahepatic resistance.[5] Haemodynamic studies demonstrate a greater reduction in portal pressure than with the utilisation of propranolol, and carvedilol can be effective even in patients not responding to propranolol.[6,7]

Present guidelines recommend NSBBs to reduce 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 red signs.[1,8] However, NSBBs are not recommended in patients without varices (pre-primary prophylaxis), those with small varices and compensated cirrhosis, or those with small varices in the absence of red signs due to a lack of evidence. This is an area that causes some controversy and requires further study.

Since clinical complications in cirrhosis are related to the severity of the portal hypertension, prevention of the escalation of portal pressure as early as possible would seem desirable, even prior to the development of varices or in patients with small varices. A large, randomised, controlled trial failed to show a beneficial effect of timolol in reducing the development of varices or variceal bleeding in patients with portal hypertension (hepatic venous pressure gradient [HVPG] ≥6 mmHg) but without varices.[9] The primary endpoint of the development of varices or variceal haemorrhage was 40% over 55 months in both arms. There were more adverse events in the timolol arm. There have been four randomised placebo-controlled trials studying the role of NSBBs in patients with small varices. Calés et al.[10] showed that propranolol in patients with small or no varices resulted in greater development of varices. However, patients without varices were included and there was a significant loss of patients at 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.[11] Sarin et al.[12] did not show any effect of propranolol in patients with small varices, despite a significant effect on portal pressure. A recent randomised placebo-controlled trial showed that carvedilol reduced the progression of varices over a minimum of 24-months

follow-up, although there was no difference in bleeding or survival.[13] In this study, patients with advanced cirrhosis and ascites were included. The promising results of carvedilol in the prevention of the progression of varices were supported by an updated meta-analysis restricted to randomised controlled trials of patients with small varices. This showed a strong trend towards reduced progression of varices with NSBBs.[14]

While all the studies to date including patients with small or no varices have focussed on preventing variceal bleeding or the development of varices as the primary endpoint, most lack adequate stratification of patients at greatest risk of developing varices or complications of cirrhosis. There is emerging data showing that prior to the development of the hyperdynamic circulation or clinically significant portal hypertension (CSPH), defined as HVPG >10 mmHg, the effect of NSBBs on reduction of portal pressure is negligible.[15] 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, which can reduce intrahepatic resistance due to alpha-1 receptor blockade. Furthermore, there is good evidence that HVPG >10 mmHg predicts development of varices.[9] This may explain the inefficacy of using NSBBs in the study of patients without varices, where the threshold for inclusion was HVPG ≥6 mmHg with a significant number of patients not having CSPH.[9] Recent studies have shown that platelet count and liver stiffness (which correlates with liver fibrosis) are useful markers for predicting those at high risk of developing varices.[16-18] Liver stiffness is measured using a modified ultrasound based technique called transient elastography (TE) and is measured in kPa. Liver stiffness has also been shown to predict the patients most likely to develop other complications of cirrhosis, such as ascites or hepatic encephalopathy.[19] In this study of patients with compensated cirrhosis, the risk of developing decompensation related to portal hypertension over a 2-year follow-up period was 53% if liver stiffness was >20 kPa. Over 50% of patients in this study had no or small varices.

Further evidence came from the cross-sectional Anticipate study,[16] which investigated the role of non-invasive tools (TE, spleen size, platelet count, platelet/spleen ratio, and liver stiffness to spleen/platelet score [LSPS]) in predicting CSPH and varices. From a total of 542 patients selected from four centres, the best non-invasive tool to predict CSPH was a LSPS ratio >2.65, which was associated with an 80% risk of CSPH. A LSPS of <1.33 or liver stiffness >20 kPa combined with a platelet count ≤150,000 was associated with a <5% risk of developing varices needing treatment. However, the non-invasive markers could not reliably identify patients with compensated cirrhosis at risk of developing varices of any size. A haemodynamic response to nadolol (>10% reduction in portal pressure) was shown to reduce ascites development by 38% over a 3-year period in patients with compensated cirrhosis and large varices, compared with non-haemodynamic responders (<10% reduction in in portal pressure).[20]

NSBBs can also have beneficial effects independent of the effects on portal pressure, with studies showing reduced risk of infections (bacterial translocation).[21] Carvedilol has anti-inflammatory, anti-oxidant, and antifibrotic properties along with other roles in enhancing insulin sensitivity and improving mitochondrial function. Since carvedilol appears to be a more potent NSBB than propranolol, with potential effects on portal pressure even in early cirrhosis due to alpha-1 receptor blockade, it seems an ideal drug to study in this setting of prevention of complications of cirrhosis and portal hypertension.[5]

It is therefore clear that there is an urgent need for large multicentre controlled trials selecting patients with compensated cirrhosis at the highest risk for the development of varices or decompensation. Ideally, HVPG measurements should be performed and patients selected if >10 mmHg i.e. CSPH. There is some evidence from an abstract that showed that NSBBs in patients (n=201) with CSPH reduced decompensation or liver related deaths, although this did not influence decompensation-free survival.[22] This may reflect the small size of the trial and its lack of power. To see a crucial effect on clinical outcomes, trials need to include several hundred or even over a thousand patients. Clearly HVPG measurements are not available in many centres and the use of TE and platelets count or LSPS ratio would seem attractive.[16-18]

The clinical trials of patients with small varices have not conclusively shown a reduction in bleeding or mortality. However, this should not dissuade further study as there will be profound clinical and economic implications if NSBBs were found to be beneficial in further large, well-designed clinical trials. The findings by Bhardwaj et al.[13] of carvedilol reducing

the progression of varices should encourage further study. These results suggest that carvedilol is the ideal NSBB to study in future trials of patients with small varices.

The key is patient stratification and large-scale multicentre involvement. All patients selected for studies on the role of NSBBs in preventing liver decompensation must have evidence of CSPH with HVPG >10 mmHg where available and/or liver stiffness/platelet count/spleen size criteria.[16] It is also important to select patients with small varices and compensated cirrhosis most likely to develop high-risk varices for entry into clinical trials using the invasive or non-invasive methods described earlier. In view of the failure rate of ≤25% of TE, alternative non-invasive methods of quantifying portal hypertension, such as non-contrast quantitative magnetic resonance imaging (MRI), should be studied.[23]

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