Editorial

Beta-blocker therapy in refractory ascites: A steady march towards the truth

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Non-selective beta-blockers (NSBB) are a mainstay for primary and secondary prophylaxes of variceal bleeding in patients with decompensated cirrhosis. Multiple international guidelines recommend their use in select patients at high risk for variceal hemorrhage.[1,2] However, the use of NSBBs in some cirrhotic patients has not been without controversy, specifically in those with refractory ascites. In the last decade, several studies have demonstrated increased mortality,[3] increased risk of the hepatorenal syndrome after an episode of spontaneous bacterial peritonitis (SBP),[4] no difference in mortality,[5] and in contrast, a survival benefit.[6] This heterogeneity of results is likely the consequence of subgroup variations and varying practice patterns highlighted by retrospective data. When closely examined it appears that when lower doses of NSBBs are used and mean arterial pressure (MAP) is largely unaffected, there is at least no significant effect, and perhaps a benefit, on overall survival in patients with refractory ascites.[5-7] Therefore, both the American Association for the Study of Liver Diseases (AASLD) and the European Association for the Study of the Liver (EASL) recommend caution in the use of NSBBs in refractory ascites, but they do not outright recommend against their use.[1,2]

Further data on the use of NSBBs in patients with refractory ascites are presented in this edition of SJG.[8] Data from a national registry in Taiwan were obtained, and 3,576 patients with cirrhosis and refractory ascites were identified. Half of these patients (n = 1,788) were prescribed propranolol, an NSBB, and the other half (n = 1,788) were not. In a univariate analysis, propranolol prescription was associated with reduced mortality and significantly longer survival as compared to patients not prescribed propranolol. These data are well in line with previous investigations on this topic, especially given the fact that the majority of patients in the Taiwanese registry were on relatively low doses of propranolol at less than 80 milligrams per day. A prior review of a national database by Bang *et al.* indicated that in patients with decompensated cirrhosis, propranolol doses of less than 160 milligrams per day are associated with improved outcomes.[7] However, the study published in this edition of the journal does clearly identify patients with refractory ascites, not simply those with decompensated cirrhosis, in whom it has been previously suggested that NSBBs could cause harm.[3] The study presented in the journal, therefore, adds some clarity to a topic, which is still hotly contested, while also leaving some questions yet unanswered.

This study suggests that NSBB use in patients with refractory ascites continues to provide the well-established benefit of reduction in severe variceal bleeding episodes, without a significant worsening of clinical outcomes in the specific subgroup of cirrhotic patients with refractory ascites. Potential mechanisms for harm of NSBBs have been proposed, largely relating to compromising the delicate hemodynamic balance in patients with decompensated cirrhosis, thereby inducing acute kidney injury, hepatorenal syndrome, or portal vein thrombosis.[4,9-11] Such mechanisms are certainly logical and plausible, especially when there are significant enough hemodynamic changes, resulting in a reduction in MAP. However, the latest data presented in the journal provide some real-world evidence that when used carefully NSBBs can continue to be effective, and not harmful. However, similar to prior investigations, this study is limited in the conclusions one can draw from it. The retrospective nature of the study does allow for an easy assessment of population-level data; however, to draw real strong conclusions, more refinement in methods will be required over time. For example, groups that did and did not receive NSBBs could not be compared based on the severity of the liver disease. It is possible that the group that did not receive NSBBs had the more severe disease at baseline, and could not receive NSBBs based on the well-established "window hypothesis" in decompensated cirrhosis, and as such, these patients would be more likely to have higher mortality rates.[12] It is also equally likely that the patients in whom NSBBs were not used had the less severe disease at baseline, which would potentially strengthen the conclusions made in the present study. Additionally, adherence rates could not be assessed, potentially allowing for significant confounding with patients in the treatment group not actually receiving the NSBB therapy. Further refinement to include nadolol and carvedilol in such an analysis would also be useful to assess for differences in

all the approved drugs for primary prophylaxis of variceal hemorrhage in the specific population of patients with refractory ascites. This would be especially useful for carvedilol, which is likely of greater risk than the NSBBs, given the additional blockade of alpha receptors. Currently, carvedilol is specifically not recommended by EASL, and not specifically mentioned by AASLD in patients with refractory ascites.[1,2]

It is clear that the question of the use of NSBBs in patients with refractory ascites remains unanswered; however, the data presented in this issue of the journal suggest that the concerns that have been previously proposed may be unfounded. This debate is far from over, and future prospective trials in this specific patient population will be needed to establish clear recommendations for NSBBs in patients with refractory ascites.

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