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Beta-blockers in cirrhosis: Therapeutic window or an aspirin for all?

To the Editor:

We have read with interest the review article by Ge and Runyon on the changing role of non-selective β-blockers (NSBBs) in cirrhosis [1]. Their role in reduction of portal hypertension is accomplished by lowering portal inflow (β1 blockade) and inducing splanchnic vasoconstriction (β2 blockade). Risk of variceal bleeding correlates also with other factors, i.e., infections and severity of liver dysfunction, suggesting absence of a pure mechanical model. For this reason, patients with more severe disease (Child-Pugh Class C) should undergo primary prophylaxis even in the presence of small varices [2].

In this paper, the authors suggested a "window hypothesis", also supported by Krag and co-authors [3], according to which NSBBs are beneficial only in decompensated patients with medium-large varices but not in patients with early or end-stage cirrhosis with refractory ascites. Their recommendation on patients with refractory ascites is mainly based on data from a study performed by Serstè and collaborators, which showed that mortality in patients with refractory ascites was increased in those taking NSBBs. The same group hypothesized that β-blockade could induce counter-regulatory over-activation of the Renin-Angiotensin-Aldosterone axis, increasing incidence of paracentesis-induced circulatory dysfunction, which could be associated with impaired renal function and reduced survival [4,5]. These data were not confirmed by another study on patients with ascites taking propranolol [6]; moreover, by analyzing all published randomized controlled trials on prophylaxis for variceal hemorrhage, bleeding unrelated mortality was similar between patients on NSBBs and those treated with other therapies in primary (277/955 *vs.* 287/1175; OR 0.91 95% CI 0.73 to 1.15) and secondary prophylaxis (188/1143 *vs.* 225/1208; OR 0.87 95% CI 0.68 to 1.12) without heterogeneity amongst studies, while causes of death were not different between patients on and off NSBBs therapy. These results were confirmed in the subgroup analysis of studies with higher prevalence of ascites (>50%) [7].

Moreover the dose of propranolol should be further investigated as a potential factor associated with increased mortality; for instance, in the French study, high propranolol doses (mean 132 mg/day) could have contributed to altered haemodynamics [8].

Furthermore, chronotropic and inotropic negative effect by NSBBs may reduce cardiac function in patients with more severe cirrhotic cardiomyopathy or new onset of sepsis. For instance, we admitted a patient with alcoholic cirrhosis on the waiting list for liver transplantation who developed spontaneous bacterial peritonitis and sepsis and required large volume paracentesis (LVP); systemic vascular resistances were severely reduced at baseline in respect of previous procedures, and at the end of LVP there was a further reduction of 31.2%; notwithstanding, a counterbalancing increase of cardiac output to 12.9 L/m (+30.9%) prevented development of hepatorenal syndrome after LVP.

With regards to their role in early cirrhosis, we recently described the pleiotropic effect of NSBBs and the need for their evaluation as part of preventative strategies in patients with early cirrhosis [9]; their potential effects include reduction in the incidence of ascites, reduction in bacterial translocation, and a potential anti-angiogenic effect [10].

NSBBs may not be a risk factor *per se* for increased non-bleeding related mortality in patients with cirrhosis and ascites. Other acquired factors such as cirrhotic cardiomyopathy or sepsis could be detrimental in those patients with refractory ascites undergoing paracentesis. Therefore, temporary dose adjustment in the event of sepsis or large volume paracentesis might prove more beneficial than not prescribing NSBBs in the first place. Further dedicated studies should evaluate NSBBs dose and their hemodynamic consequences, to provide hepatologists with conclusive evidence between the possible increase in mortality and the use of NSBBs.

Conflict of interest

The authors declared that they do not have anything to disclose regarding funding or conflict of interest with respect to this manuscript.

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An apology for beta blockers

To the Editor:
We read with interest the recent review on beta-blockers in cirrhosis by Ge and Runyon [1]. This topic is of great importance, as non-selective beta blockers are a pharmacological mainstay in the management of patients with cirrhosis; the amount of evidence has been increasing substantially since the first published trial of their use in the prevention of variceal bleeding [2], particularly in recent years.

In their review, the authors dedicate a sub-heading to "Benefits of beta-blocker therapy". This consists of only two paragraphs, in which some trials of beta blockade for primary prevention of variceal bleeding are discussed. In the last line, the use of beta blockers in secondary prophylaxis of variceal bleeding is just about mentioned, and reference to a table (Table 1) is made. Table 1, titled "Key studies supporting beta-blocker usage", only lists trials of beta blockers for the primary prevention of variceal bleeding. For reasons best known to them (but not to us), the authors chose to completely ignore mountains of evidence for a wide range of non-selective beta blockers in patients with cirrhosis, including such trivialities as effects on mortality, risk of decompensation, development of ascites, renal failure, encephalopathy, and bacterial infections. This includes true landmark studies [3], the results of which have both been replicated [4] and extensively discussed in the literature [5]. Similarly, the vast majority of the wide-ranging pharmacological effects of beta-blockers, particularly non-haemodynamic effects [5,6], are largely ignored, exception made for a single mentioning of bacterial translocation in Fig. 1.

The authors then embark on a lengthy discussion of "adverse effects of beta-blocker therapy". The sub-heading itself spans 5 paragraphs (more than twice the length of the benefits!), but the successive elaboration on the inherent evil of beta blockers (variously termed "The differential effect of beta-blockers in cirrhosis", "Blood pressure and survival", "Beta-blockers in refractory ascites", and "Additional challenges of beta-blocker therapy") cover several pages. In this section, the authors discuss at length the possible adverse effects of beta blockers, quoting studies in patients without liver disease published mainly between 1969 and 1990. It is also rather puzzling that the use of beta blockers in arterial hypertension, cardiac failure, and acute coronary syndromes is discussed, as this debate has little importance to their use in liver disease. Interestingly, had the authors applied a bit more dedication to their "holistic" approach to beta-blockers, they might have stumbled across other rather informative (and much more recent) studies outlining the safety (and significant benefit) of beta blockers in COPD [7,8], peripheral vascular disease [9], and diabetes [10]. Table 2, titled "Key studies suggesting potential harm from beta-blocker usage" clearly is meant to mirror Table 1 in size and importance. It strikes us that of the "key" studies mentioned in this table, the first only shows an increased likelihood of adverse events with beta blockers as compared to placebo (a finding which is hardly surprising), while the second study quite amusingly only investigates the prognostic importance of the cardiac index in cirrhosis without making use of beta blockers. The other two quoted studies are a heavily debated observational study and a cross-over study looking at paracentesis-induced circulatory dysfunction in 10 patients. By contrast, even the completely unrepresentative choice of key studies in Table 1 entirely consists of controlled trials.

At this point it is of little further consequence to mention other surprising findings, such as the space given to the discussion of midodrine and ACE inhibitors in a review on beta blockers, and the fact that studies on midodrine are quoted as evidence "confirming the importance of maintaining cardiac output in patients with advanced cirrhosis" – indeed, midodrine is a vasoconstricting agent and does not increase cardiac output, but has actually been found to decrease it [11].

Finally, in their fervour against beta-blockers, the authors go as far as providing "recommendations" for the use of beta blockers in cirrhosis, the evidence for which is as feeble as the discussion leading up to it. Needless to say, these are to our mind very hazardous statements, which might well lead to a reduction in the use of this class of highly effective and very cheap agents, which have rightly been termed "the Hepatologist's Aspirin" [12].

Sadly, we feel that a great opportunity to discuss this crucial topic in Hepatology has been missed, as this review is ill-conceived and poorly researched, leading to conclusions which might be far more harmful than any effect beta blockers might have in patients with cirrhosis.

Conflict of interest

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