Use of Non-selective Beta-blockers in Decompensated Cirrhosis: Controversy Continues

ABSTRACT 1

J Hepatol. Online first (doi:10.1016/j.jhep.2015.10.018).
Reference: JHEPAT 5868

Treatment with non-selective beta-blockers is associated with reduced severity of systemic inflammation and improved survival of patients with acute-on-chronic liver failure

Rajeshwar P. Mookerjee¹, Marco Pavesi², Karen Louise Thomsen¹, Gautam Mehta¹, Jane Macnaughtan¹, Flemming Bendtsen³, Minneke Coenraad⁴, Jan Sperl⁵, Pere Gines^{6,7,8,9}, Richard Moreau¹⁰, Vicente Arroyo², Rajiv Jalan¹

¹Liver Failure Group, UCL Institute for Liver and Digestive Health, UCL Medical School, Royal Free Hospital, London, United Kingdom. ²Liver Unit/EASL-CLIF Data Center, Hospital Clínic de Barcelona, Barcelona, Spain. ³Department of Gastroenterology, Hvidovre Hospital, University of Copenhagen, Copenhagen, Denmark. ⁴Department of Gastroenterology-Hepatology, Leiden University Medical Center, Leiden, the Netherlands. ⁵Department of Hepatogastroenterology, Institute for Clinical and Experimental Medicine, Prague, Czech Republic. ⁶Liver Unit, Hospital Clínic de Barcelona, University de Barcelona, Barcelona, Spain. ⁷University of Barcelona, Barcelona, Spain. ⁸Institut d'Investigacions Biomediques August Pi I Sunyer (IDIBAPS), Barcelona, Spain. ⁹Centro d'Investigación Biomédica en Red Enfermedades Hepáticas y Digestivas (CIBERehd), Barcelona, Spain. ¹⁰Inserm, U1149, Centre de Recherche sur l'Inflammation (CRI), Clichy and Paris, France; UMRS1149, Université Paris Diderot-Paris 7, Paris, France; Département Hospitalo-Universitaire (DHU) UNITY, Service d'Hépatologie, Hôpital Beaujon, Assistance Publique-Hôpitaux de Paris, Clichy, France; Laboratoire d'Excellence Inflamex, PRES Sorbonne Paris Cité, Paris, France.

Background and aims: Non-selective beta-blockers (NSBBs) have been shown to have deleterious outcomes in patients with refractory ascites, alcoholic hepatitis and spontaneous bacterial peritonitis leading many physicians to stop the drug in these cases. Acute on chronic liver failure (ACLF) is characterized by systemic inflammation and high mortality. As NSBBs may have beneficial effects

on gut motility and permeability and, systemic inflammation, the aims of this prospective, observational study were to determine whether on-going use of NSBBs reduced 28-day mortality in ACLF patients.

Methods: The study was performed in 349 patients with ACLF included in the CANONIC study, which is a prospective observational investigation in hospitalized cirrhotic patients with acute deterioration. The data about the use of NSBBs, its type and dosage was specifically recorded. Patient characteristics at enrollment significantly associated with treatment and mortality were taken into account as potential confounders to adjust for treatment effect. A logistic regression model was fitted.

Results: 164 (47%) ACLF patients received NSBBs whereas 185 patients did not. Although the CLIF-C ACLF scores were similar at presentation, more patients in the NSBB treated group had lower grades of ACLF ($P = 0.047$) at presentation and significantly more patients improved. Forty patients (24.4%) died in NSBB treated group compared with 63 patients (34.1%) ($P = 0.048$) [estimated risk-reduction 0.596 (95%CI: 0.361–0.985; $P = 0.0436$)]. This improvement in survival was associated with a significantly lower white cell count (NSBB: 8.5 (5.8); no NSBB: 10.8 (6.6); $P = 0.002$). No long-term improvement in survival was observed.

Conclusions: This study shows for the first time that ongoing treatment with NSBBs in cirrhosis is safe and reduces the mortality if they develop ACLF. Careful thought should be given before stopping NSBBs in cirrhotic patients.

ABSTRACT 2

Gut. 2015;64:1111–1119. doi:10.1136/gutjnl-2013-306502

Non-selective β -blockers are associated with improved survival in patients with ascites listed for liver transplantation

Joanna A Leithead^{1,2}, Neil Rajoriya¹, Nadeem Tehami¹, James Hodson³, Bridget K. Gunson^{1,2}, Dhiraj Tripathi¹, James W. Ferguson¹

¹Liver Unit, Queen Elizabeth Hospital, Birmingham, UK. ²NIHR Biomedical Research Unit and Centre for Liver Research, University of Birmingham, Birmingham, UK. ³Department of Statistics, Wolfson Building, Queen Elizabeth Hospital, Birmingham, UK

Objective: Recent data have suggested that non-selective β -blockers (NSBB) are associated with increased mortality in patients with cirrhosis and refractory ascites. However, other evidence implies that NSBB may be beneficial in this setting by reducing bacterial translocation. Our aim was to determine whether NSBB use was a risk factor for mortality in patients with end-stage chronic liver disease and ascites awaiting liver transplantation.

Design: This was a single-centre retrospective study of 322 patients with ascites listed January 2007 to July 2011.

Results: NSBB patients ($n = 159$) and non-NSBB patients ($n = 163$) were comparable with regards to listing model for end-stage liver disease score ($P = 0.168$), frequency of hepatocellular carcinoma ($P = 0.193$) and refractory ascites (35.2% vs. 37.4%, $P = 0.681$). 82 patients died, 221 patients were transplanted and 19 patients were removed from the list during a median follow-up duration of 72 days; the median time to death was 150 and 54 days in the NSBB and non-NSBB groups, respectively. In a multivariate competing risk Cox model, patients on NSBB had reduced mortality compared with propensity risk score-matched non-NSBB patients (HR 0.55; 95% CI 0.32–0.95, $P = 0.032$). Similarly, in the subgroup of patients with refractory ascites ($n = 117$), NSBB remained independently associated with less wait list death (adjusted HR 0.35; 95% CI 0.14–0.86, $P = 0.022$).

Conclusions: NSBB in patients with ascites and refractory ascites listed for liver transplantation are not detrimental, and instead are associated with reduced waitlist death. Our findings argue that NSBB are safe and may confer benefit in patients with ascites complicating end-stage liver disease.

COMMENTS

Non-selective beta-blockers (NSBBs) including propranolol are recommended as first-line therapy in both primary and secondary prophylaxis of oesophageal variceal bleeding.¹ The mechanism of action of NSBB includes antagonism of both β -1 receptors (reduction in cardiac output) and β -2 receptors (splanchnic vasoconstriction). This in turn leads to a reduction in portal flow, and reduction in the risk of variceal bleeding. Till date, numerous publications have reported a beneficial role of beta-blockers in the primary and secondary prophylaxis of variceal bleeding. It is important to note that most randomized control trials (RCTs) excluded patients with refractory ascites. There is a lack of data regarding the effectiveness of these drugs in a subset of patients with advanced (decompensated) cirrhosis including refractory ascites and associated complications like spontaneous bacterial peritonitis.

The group from France led by Didier Lebrech (1981), in an RCT, reported the effectiveness of propranolol in the prevention of recurrent variceal bleeding.² Thereafter, multiple studies showed similar results. A large controversy arose when the same group, in a subsequent observation study published in *Hepatology* 2010, documented poor survival in patients with refractory ascites.³ In this single centre, observational study, 151 patients were included prospectively. All patients were on regular large volume paracentesis and intravenous albumin administration. There were no differences in the baseline characteristics of the two groups. The median survival of patients on NSBBs was lower as compared to patients not on NSBBs (5 months vs 20 months; $P = 0.0001$). In addition, on

multivariate analysis, NSBBs were independently associated with mortality. Important limitations of this study include its study design (case-control). Secondly, the causes of death in two-third of the patients included sepsis or HCC, which were attributed to propranolol.

Furthermore, the role of beta-blockers was further challenged in another study by Mandorfer et al.⁴ In this retrospective analysis of patients with decompensated cirrhosis, among patients with SBP, treatment with NSBBs resulted in reduced transplant-free survival (HR = 1.58; $P = 0.014$) and increased days of non-elective hospitalization (NSBBs 29.6 days/person-year vs not on NSBBs 23.7 days/person-year). In addition, among patients on NSBBs, there was a higher incidence of hepatorenal syndrome and AKI.

The mechanism underlying this harmful effect is due to the effect of NSBBs on the heart (β -1 antagonism). The pathophysiology associated with the development of refractory ascites includes peripheral vasodilation, activation of the renin-angiotensin-aldosterone system and renal sodium and water retention. This in turn leads to increase in heart rate and cardiac output. The NSBBs, through β -1 antagonism, at this stage lead to a reduction in cardiac output, hypotension, reduced renal perfusion, hepatorenal syndrome and death.

Ideally, an RCT is the best evidence to show the real efficacy of the drug. Two recent studies, one prospective and another retrospective, suggest that NSBBs may not be as sinister as what was suggested by the results of Serste et al.³ Mookerjee et al.⁵ analyzed the data of CANONIC study, which involved prospective analysis of 1349 cirrhotic patients from 29 European hospitals.⁶ Of the 349 ACLF patients, 164 (47%) were on NSBBs, and the remaining 185 patients did not receive NSBBs. The patients receiving NSBBs were older and had a higher frequency of prior episodes of decompensation (GI bleed was more frequent in patients receiving NSBBs). The bilirubin levels and total leucocyte counts were significantly lower in patients receiving NSBBs. During the follow-up course, 3–7 days after diagnosis, prevalence of cerebral and coagulation failure was significantly lower in patients receiving NSBBs. There were no differences in the rest of the organ failures. In patients receiving NSBBs, there was a higher prevalence of ACLF-1, whereas, in patients not receiving NSBBs, there was a higher frequency of ACLF-2 and ACLF-3. In addition, 23.4% not taking NSBBs had worsening of ACLF grade as compared to 14.2% in the NSBBs group ($P = 0.0371$). Furthermore, among patients on NSBBs, there was a higher frequency of complete resolution as compared with those not on NSBBs. Short-term mortality was significantly higher in patients receiving NSBBs, whereas 6-month and 1-year mortality were similar between the two groups.

Leithead et al.⁷ in a retrospective analysis evaluated the effect of NSBBs on patients with ascites (including refractory ascites) listed for liver transplantation. Of the 322

patients, 159 (49.4%) were on NSBBs. As expected, at baseline, patients with NSBBs had a higher frequency of prior variceal bleeding. The median time to death was lower in patients on NSBBs than in patients not on NSBBs (159 days vs 52 days). On propensity score matching, use of NSBBs was associated with a reduced risk of mortality in patients with ascites (including refractory ascites). The major limitation of this study is its retrospective design.

The data from these 2 recent studies suggest that NSBBs may, in fact, be beneficial in patients with refractory ascites, which is in contrast to the results of Serste et al.³

We still have more to see from this Pandora's box and the last word about the role of NSBBs has not been said as yet. The NSBBs may be cautiously used in a subset of patients till more data emerge from well-designed prospective studies.

CONFLICTS OF INTEREST

The author has none to declare.

REFERENCES

1. de Franchis R. Expanding consensus in portal hypertension: report of the Baveno VI Consensus Workshop: stratifying risk and individualizing care for portal hypertension. *J Hepatol.* 2015;63(3):743–752 [Epub 2015/06/07].
2. Lebrec D, Poynard T, Hillon P, Benhamou JP. Propranolol for prevention of recurrent gastrointestinal bleeding in patients with cirrhosis: a controlled study. *N Engl J Med.* 1981;305(23):1371–1374 [Epub 1981/12/03].
3. Serste T, Melot C, Francoz C, et al. Deleterious effects of beta-blockers on survival in patients with cirrhosis and refractory ascites. *Hepatology.* 2010;52(3):1017–1022 [Epub 2010/06/29].
4. Mandorfer M, Bota S, Schwabl P, et al. Nonselective beta blockers increase risk for hepatorenal syndrome and death in patients with cirrhosis and spontaneous bacterial peritonitis. *Gastroenterology.* 2014;146(7):1680 e1–1690 e1 [Epub 2014/03/19].
5. Mookerjee RP, Pavesi M, Thomsen KL, et al. Treatment with non-selective beta-blockers is associated with reduced severity of systemic inflammation and improved survival of patients with acute-on-chronic liver failure. *J Hepatol.* 2015. <http://dx.doi.org/10.1016/j.jhep.2015.10.018>.
6. Moreau R, Jalan R, Gines P, et al. Acute-on-chronic liver failure is a distinct syndrome that develops in patients with acute decompensation of cirrhosis. *Gastroenterology.* 2013;144(7):1426–1437. 37 e1–9 [Epub 2013/03/12].
7. Leithead JA, Rajoriya N, Tehami N, et al. Non-selective beta-blockers are associated with improved survival in patients with ascites listed for liver transplantation. *Gut.* 2015;64(7):1111–1119 [Epub 2014/10/05].

Shalimar

*All India Institute of Medical Sciences, Department of
Gastroenterology, New Delhi, India
E-mail address: drshalimar@yahoo.com*