Research Article

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Cirrhosis

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☆

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Background & 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 ongoing 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.

Keywords: Acute-on-chronic liver failure; Cirrhosis; Multi-organ failure; Sepsis; Prognosis; Non-selective beta blockers.

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Abbreviations: ACLF, acute-on-chronic liver failure; AD, acute decompensation; CANONIC study, EASL-CLIF acute-on-chronic liver failure study; CLIF, chronic liver failure; CLIF-C ACLFs, CLIF consortium ACLF score; CLIF-C OFs, CLIF consortium organ failure score; CLIF-SOFAs, CLIF-sequential organ failure assessment score; CPs, Child-Pugh score; E, epinephrine; EASL, European Association for the Study of the Liver; FIO_2, fraction of inspired oxygen; HE, hepatic encephalopathy; INR, international normalized ratio; MAP, mean arterial pressure; MELDs, model of end-stage liver disease; MELD-Nas, MELD-sodium score; NE, norepinephrine, PaO_2, partial pressure of arterial oxygen; SOFA, sequential organ failure assessment; SpO_2, pulse oximetric saturation.

Introduction

Acute-on-chronic liver failure (ACLF) is a recently defined entity characterized by acute deterioration of liver function, multi-organ failure and high mortality [1–4]. A characteristic feature of this syndrome is systemic inflammation, the severity of which is an independent predictor of mortality [4,5]. The mechanism(s) underlying this severe systemic inflammation is unknown. The use of classical anti-inflammatory agents, such as anti-tumour

necrosis factor or steroids in ACLF is fraught with potential difficulties as infection and immune failure are also important features of this syndrome and when present, is associated with a high risk of mortality [2,5–7]. Treatment of ACLF is an unmet need and modulation of inflammatory response in ACLF is an important potential target of therapy [8].

Recently, much controversy has arisen in the literature due to the suggestion that the use of non-selective beta blockers (NSBBs) in patients with refractory ascites [9,10], spontaneous bacterial peritonitis [11] and alcoholic hepatitis [12], may increase mortality rates through accentuation of circulatory disturbances and the resultant renal failure. These studies are limited in their design as they address specific subgroups of patients such as refractory ascites and spontaneous bacterial peritonitis and lack prospective data assessing extrahepatic, extrarenal organ functions as well as overall severity using prognostic scores other than liver-specific scores. Despite these limitations, many clinicians are ceasing to use this potentially lifesaving drug in patients with advanced cirrhosis despite another study suggesting improved outcomes for patients on the waiting list for liver transplantation [13].

NSBBs have been studied extensively in cirrhotic patients and are the drug of first choice for primary and secondary prophylaxis of variceal bleeding, as it has been incontrovertibly shown to have beneficial effects on the severity of portal hypertension [14]. These effects require both the beta-1 and beta-2 actions of the drug to ameliorate splanchnic vasodilation and high cardiac output [15]. NSBBs have many other potential beneficial actions in patients with cirrhosis through its action on increasing gut motility and reducing bacterial translocation, which would reduce systemic inflammation and therefore have beneficial effects in ACLF patients over and above its hemodynamic effects [16,17].

This study was designed to test the hypothesis that cirrhotic patients being treated with NSBBs would have reduced systemic inflammation and reduced mortality if they developed ACLF. In order to test this, we used the data from the CANONIC study, which is a prospective, observational study performed in 1349 cirrhotic patients included from 29 European hospitals [2]. The present analysis is focused on the ACLF cohort. The data from this study was previously used to derive the diagnostic and prognostic criteria for ACLF, which were validated in independent cohorts [2–4]. The specific aims of this study were to evaluate the clinical effects of ongoing administration of NSBBs in hospitalized cirrhotic patients who developed ACLF, focusing on safety of its use, effects on organ function and mortality, clinical course of ACLF and effects on inflammatory markers.

Table 1. Characteristics at ACLF diagnosis in patients receiving and not receiving NSBBs within the previous 3 months.

Characteristics	No NSBB N = 185	Use of NSBBs N = 164	*p* value
Age (yr)	53.6 (11.5)	58.1 (11.8)	0.0003
Male sex	117 (63.2%)	111 (67.7%)	0.3844
Cause of cirrhosis:			
Alcohol alone	113 (62.4%)	85 (54.1%)	0.1228
HCV alone	22 (12.2%)	26 (16.6%)	0.2471
HCV + alcohol	20 (11.1%)	11 (7.0%)	0.1990
Previous decompensations	116 (65.5%)	137 (86.7%)	<0.0001
Ascites	102 (87.9%)	118 (86.8%)	0.7817
Hepatic encephalopathy	56 (49.1%)	66 (49.6%)	0.9374
Gastrointestinal bleeding	19 (16.8%)	58 (43.3%)	<0.0001
Spontaneous bacterial peritonitis	19 (17.3%)	20 (15.5%)	0.7122
Other	23 (20.7%)	26 (19.9%)	0.8662
Potential precipitating events of ACLF:			
At least one PE	110 (62.2%)	95 (59.8%)	0.6527
>1 PE	41 (23.2%)	26 (16.4%)	0.1187
Bacterial infection	57 (30.8%)	53 (32.3%)	0.7624
Gastrointestinal hemorrhage	31 (16.8%)	22 (13.4%)	0.3852
Active alcoholism before admission	50 (28.9%)	28 (18.1%)	0.0214
Other PEs	13 (7.3%)	13 (8.3%)	0.7388
Ascites clinically diagnosed	149 (81.0%)	119 (73.0%)	0.0771
Ascites + subrogates of ascites	177 (95.7%)	158 (96.3%)	0.7517
Mean arterial pressure (mmHg)	78.9 (12.7)	78.2 (13.3)	0.6639
Heart rate (bpm)	89.8 (19.0)	79.0 (19.5)	<0.0001
Organ failures:			
Liver	80 (43.2%)	57 (34.8%)	0.1051
Kidney	89 (48.1%)	89 (54.3%)	0.2506
Cerebral	51 (27.6%)	30 (18.3%)	0.0405
Coagulation	66 (35.7%)	42 (25.6%)	0.0423
Circulation	35 (18.9%)	27 (16.5%)	0.5492
Lungs	19 (10.3%)	19 (11.6%)	0.6938
Kidney dysfunction	35 (22.2%)	19 (13.8%)	0.0624
Mild to moderate hepatic encephalopathy	54 (34.2%)	51 (37.0%)	0.6281
CLIF-C ACLF score	51.4 (10.2)	49.5 (10.0)	0.1468
MELD score	28.9 (7.4)	27.1 (7.6)	0.0546
Laboratory data:			
Hematocrit (%)	27 (5)	27 (5)	0.6888
Platelet count (x10^9/L)	97 (77)	81 (60)	0.0492
Serum bilirubin (mg/dl)	13.8 (11.9)	10.1 (11.0)	0.0072
International normalized ratio	2.3 (1.0)	2.2 (1.0)	0.3580
Alanine aminotransferase (U/L)	35 (22-66)	34 (21-66)	0.5149
Aspartate aminotransferase (U/L)	77 (41-143)	68 (35-123)	0.4698
γ-Glutamyltransferase (U/L)	77 (30-151)	70 (36-138)	0.6451
Serum creatinine (mg/dl)	2.0 (1.4)	2.1 (1.3)	0.4328
Serum sodium (mmol/L)	134.3 (6.7)	136.0 (6.1)	0.0199
WBC (x10^9/L)	10.8 (6.6)	8.5 (5.8)	0.0021
Plasma C-reactive protein (mg/L)	33.5 (16-54)	25.4 (13-52)	0.4664
ACLF grade:			
ACLF-1	81 (43.8%)	91 (55.5%)	
ACLF-2	73 (39.5%)	57 (34.8%)	
ACLF-3	31 (16.7%)	16 (9.7%)	0.0474
Liver transplantation after 28 days	15 (8.1%)	17 (10.4%)	0.2009
Liver transplantation after 90 days	24 (13.1%)	26 (16.2)	0.4660
28-day mortality	63 (34.1%)	40 (24.4%)	0.0482
90-day mortality	83 (44.9%)	63 (38.4%)	0.2228

Data are n (%), mean (standard deviation) or median (Inter-quartile range).
NSBBs, non-selective beta blockers.