I. Beta-blockers: Finding the Right Timing and its Role in Cirrhosis

Hernández-Gea V, Aracil C, Colomo A, et al.
Development of Ascites in Compensated Cirrhosis with Severe Portal Hypertension Treated with β -blockers.
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Abstract

Objectives: In compensated cirrhosis, a threshold value of hepatic venous pressure gradient (HVPG) ≥ 10 mmHg is required for the development of decompensation. However, whether the treatment of portal hypertension (PHT) can prevent the transition into development of ascites once this level has been reached is unclear. Our aim was to assess the relationship between changes in HVPG induced by beta-blockers and development of ascites in compensated cirrhosis with severe PHT. **Methods:** Eighty-three patients without any previous decompensation of cirrhosis with large esophageal varices and HVPG ≥ 12 mmHg were included. After baseline hemodynamic measurements nadolol was administered and a second hemodynamic study was repeated 1–3 months later. **Results:** During 53 ± 30 months of follow-up, decompensation occurred in 52 patients (62%) and in 81% of them, ascites was the first manifestation. Using receiver operating characteristic curve analysis, a decrease in HVPG $\geq 10\%$ was the best cut-off to predict ascites. As compared with nonresponders, patients with an HVPG decrease $\geq 10\%$ had a lower probability of developing ascites (19% vs 57% at 3 years, $P < 0.001$), refractory ascites ($P = 0.007$), and hepatorenal syndrome ($P = 0.027$). By Cox regression analysis hemodynamic nonresponse was the best predictor of ascites. By stepwise logistic regression, development of ascites was independently associated with nonresponse, whereas refractory ascites, hepatorenal syndrome, and spontaneous

bacterial peritonitis were not. **Conclusion:** In patients with compensated cirrhosis and large varices treated with beta-blockers, an HVPG decrease $\geq 10\%$ significantly reduces the risk of developing ascitic decompensation and other related complications such as refractory ascites or hepatorenal syndrome.

COMMENT

It was more than 30 years back Lebrec et al¹ proposed the role of propranolol in portal hypertension and nonselective beta-blockers became the treatment of choice for the primary prophylaxis of variceal bleeding. The role of beta-blockers in portal hypertension has recently however come under threat. Firstly, evaluation of beta-blockers in prevention of development of ascites has not shown any benefit.² Secondly, in primary prophylaxis of variceal bleed, some studies have reported lower rates of bleeding in patients treated with endoscopic variceal ligation (EVL) compared to beta-blockers.^{3,4} Thirdly, in advanced cirrhosis with refractory ascites, patients treated with propranolol have been found to have lower survival compared to patients not treated with propranolol.⁵ Sersté et al⁶ have shown that use of beta-blockers may be associated with a high-risk of paracentesis-induced circulatory dysfunction in patients with cirrhosis and refractory ascites.

So with beta-blockers not effective in early portal hypertension to prevent development of varices; their role threatened in preventing variceal bleeding by EVL; and possibly detrimental in advanced decompensated cirrhosis with refractory ascites; the current study by Hernández-Gea et al⁷ re-enforces the role of beta-blockers in cirrhosis. Their study suggests that starting the non-selective beta-blocker nadolol in patients with cirrhosis and high-risk varices can delay the development of ascitic decompensation.

The beneficial effect of beta-blockers in decreasing risk of development of ascites however comes with some riders. The current study included compensated patients with large varices. It still remains to be seen if beta-blockers will also be effective in patients without varices/early varices or decompensated patients. The beneficial effect was only seen in patients with HVPG decrease of $\geq 10\%$ from baseline, an effect seen in only about half the patients. The use of beta-blockers is associated with significant side effects and resulting in drug discontinuation of the drug. The lack of efficacy of beta-blockers is compounded by the poor tolerability of the drug in higher doses and many patients discontinue the drug due to side effects. This may decrease the beneficial effect of beta-blockers in not only

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Abbreviations: ALF: acute liver failure; ALFED: ALF early dynamic; EVL: endoscopic variceal ligation; HVPG: hepatic venous pressure gradient; INR: international normalized ratio; MELD: model for end-stage liver disease; OR: odds ratio; PHT: portal hypertension

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preventing variceal bleed but also in the prevention of ascites. The current study did not have a placebo arm without beta-blockers, which would have strengthened the role of the drugs.

Testing for HVPG may not be feasible in routine clinical practice to identify likely responders. So what is the advice to the practicing clinician as to the use of beta-blockers in cirrhotics? Should they give it across the board to all patients with cirrhosis? The answer may lie in identifying the stage of cirrhosis. As on date there is no role of beta-blockers in cirrhotics without varices. In compensated patients with varices, use of beta-blockers could be used even if HVPG measurements are not feasible to prevent variceal bleed and delay the development of ascites, more so in those with large varices. This current study tilts the EVL vs beta-blocker debate in prophylaxis of variceal bleed in favor of the latter. However, in advanced decompensated cirrhosis with refractory ascites, beta-blockers should be used with caution.

REFERENCES

1. Lebrec D, Poynard T, Hillon P, Benhamou JP. Propranolol for prevention of gastrointestinal bleeding in patients with cirrhosis. A controlled study. *N Engl J Med* 1981;305:1371–4.
2. Groszmann RJ, Garcia-Tsao G, Bosch J, et al. Beta-blockers to prevent gastroesophageal varices in patients with cirrhosis. *N Engl J Med* 2005;353:2254–61.
3. Sarin SK, Lamba GS, Kumar M, Misra A, Murthy NS. Comparison of endoscopic ligation and propranolol for the primary prevention of variceal bleeding. *N Engl J Med* 1999;340:988–93.
4. Jutabha R, Jensen DM, Martin P, Savides T, Han SH, Gornbein J. Randomized study comparing banding and propranolol to prevent initial variceal hemorrhage in cirrhotics with high-risk esophageal varices. *Gastroenterology* 2005;128:870–81.
5. Sersté T, Melot C, Francoz C, et al. Deleterious effects of b-blockers on survival in patients with cirrhosis and refractory ascites. *Hepatology* 2010;52:1017–22.
6. Sersté T, Francoz C, Durand F, et al. Beta-blockers cause paracentesis-induced circulatory dysfunction in patients with cirrhosis and refractory ascites: a cross-over study. *J Hepatol* 2011;55:794–9.
7. Hernández-Gea V, Aracil C, Colomo A, et al. Development of ascites in compensated cirrhosis with severe portal hypertension treated with β -blockers. *Am J Gastroenterol* 2012;107:418–27.

II. Ammonia in Acute Liver Failure: If the Level Does Not Decline, the Outcome of Acute Liver Failure Might

Kumar R, Shalimar, Sharma H, et al. Persistent Hyperammonemia is Associated with Complications and Poor Outcomes in Patients with Acute Liver Failure. *Clin Gastroenterol Hepatol* 2012
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Abstract

Background and Aims: Patients admitted to the hospital with acute liver failure (ALF) and high arterial levels of ammonia are more likely than patients with lower levels of ammonia to have complications and poor outcomes. Acute liver failure is dynamic process; ammonia levels can change over time. We investigated whether early changes (first 3 days after admission) in arterial levels of ammonia were associated with complications and outcomes, and identified factors associated with persistent hyperammonemia. **Methods:** We performed a prospective observational study, measuring arterial ammonia levels each day, for 5 days, in 295 consecutive patients with ALF. We analyzed associations of changes in ammonia levels during first 3 days with complications and outcomes. **Results:** Patients with persistent arterial hyperammonemia ($\geq 122 \mu\text{mol/L}$ for 3 consecutive days), compared to those with decreasing levels, had lower rates of survival (23% vs 72%; $P < 0.001$) and higher percentages of

cerebral edema (71% vs 37%; $P < 0.001$) infection (67% vs 28%; $P = 0.003$) and seizures (41% vs 7.7%; $P < 0.001$). Patients with persistent hyperammonemia had greater mortality, with an odds ratio (OR) of 10.7, compared to patients with baseline levels of ammonia $\geq 122 \mu\text{mol/L}$ (OR, 2.4). Patients with persistent hyperammonemia were more likely to progress to and maintain advanced hepatic encephalopathy than those with decreasing levels. Patients with persistent, mild hyperammonemia ($\geq 85 \mu\text{mol/L}$ for 3 days) were also more likely to have complications or die ($P < 0.001$) than patients with serial ammonia levels $< 85 \mu\text{mol/L}$. Infections (OR, 4.17), renal failure (OR, 2.20), and decreased arterial pH (OR, 0.003) were independent predictors of persistent hyperammonemia. **Conclusion:** Patients with ALF and persistent arterial hyperammonemia for 3 days after admission are more likely to develop complications and have greater mortality than patients with decreasing levels or high baseline levels. Infection, renal failure, and decreased arterial pH are independent predictors of persistent hyperammonemia.

COMMENT

While ammonia neurotoxicity has always been at the center stage of pathogenesis of hepatic encephalopathy and liver failure, there had been limited data of ammonia levels in relation to cerebral dysfunction or patient outcome in acute liver failure (ALF). In 2006, Kumar et al¹ had shown that arterial ammonia at presentation was predictive of outcome and could be used for risk stratification. Continuing further in their research of ammonia and liver failure, the same group of Acharya research team has evaluated the value of serial ammonia levels in ALF.²