Beta-blockers in cirrhosis: Cons

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1) Are beta-blockers always indicated to prevent variceal hemorrhage in cirrhotic patients?

2) Can beta-blockers be safely used at all stages of cirrhosis?

3) Which subset of cirrhotic patients could benefit the most from beta-blocker therapy?
1) Are beta-blockers always indicated to prevent variceal hemorrhage in cirrhotic patients?
Beta-blocker therapy and prevention of gastroesophageal varices

- 213 cirrhotic patients with portal hypertension (HVPG ≥ 6 mmHg)
- Randomized to receive either placebo (n=105) or NSBB (timolol) [n=108]
- Primary end point: development of gastroesophageal varices or variceal bleeding

• Adverse events were significantly higher in the timolol group (48% vs. 32%)

Groszmann et al. NEJM 2005
Adherence to beta-blocker therapy

• Despite well established guidelines and recommendations, as few as 6–22% of patients with known medium or large varices received primary prophylaxis with beta-blockers\(^1\).

• **Side effects** led to treatment discontinuation in approximately 15% of patients in the various beta-blocker trials in patients with cirrhosis\(^2\).

<table>
<thead>
<tr>
<th>Cardiac</th>
<th>Non-cardiac</th>
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<tbody>
<tr>
<td>Symptomatic bradycardia</td>
<td>Fatigue</td>
</tr>
<tr>
<td>Exacerbation/precipitation of heart failure</td>
<td>Headaches, dizziness</td>
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<tr>
<td>High grade heart block</td>
<td>Erectile dysfunction</td>
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<td></td>
<td>Cold extremities, claudication</td>
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<tr>
<td></td>
<td>Shortness of breath</td>
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\(^1\)Mellinger et al. *Clin Gastroenterol Hepatol* 2013
\(^2\)Garcia-Tsao et al. *Am J Gastroenterol* 2009
Pathophysiology of portal hypertension in cirrhosis

- Intra-hepatic resistance to blood flow
- Portal hypertension
- Hyperproduction of nitric oxide and other mediators
- Peripheral arterial vasodilatation
- Effective arterial blood volume
- Sympathetic nervous system
- Renin-angiotensin-aldosterone system
- Cardiac output
- Vasoconstriction of renal circulation
- Water and salt-retaining mechanisms
- Ascites

↑ Cardiac output
↑ Vasoconstriction of renal circulation
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↓ Water and salt-retaining mechanisms
Schrier et al. Hepatology 1988
Pharmacological effects of beta-blockers

**NSBB** (e.g. propranolol, nadolol, timolol)

- **β1-receptor**
- **β2-receptor**

- **Vasoconstriction**
- **↑ Portal pressure**
- **↓ Cardiac output**

**Less effective and not recommended for the prophylaxis of variceal hemorrhage**

- **β1-antagonists**, (e.g. atenolol, metoprolol)

Hilton et al. *Hepatology*, 1982
Westaby et al. *Gut*, 1985
2) Can beta-blockers be safely used at all stages of cirrhosis?
Why could NSBB be harmful?

- Studies in patients without NSBB established an association between blood pressure and survival.
- 139 patients with cirrhosis and ascites, mean follow-up of 12.8 months.

**Hypothesis**: as cirrhosis progresses, the cardiovascular system loses its compensatory ability.

Llach et al. *Gastroenterology* 1988
Low cardiac output and MAP are associated with a worse prognosis in cirrhotic patients

- 24 patients with cirrhosis and ascites without NSBB

Beta-blockers may worsen hemodynamics resulting in subsequent mortality

Krag et al. Gut 2010
Deleterious effects of NSBB in cirrhotics with refractory ascites

- One prospective non-randomized study included 151 cirrhotic patients with refractory ascites and frequent large-volume paracentesis with intravenous albumin administration.
- Patients given NSBB were not significantly different from the others (MELD, Child-Pugh score).

![Graph showing survival rates with and without beta-blockers.](image)

- Survival rates for patients with and without beta-blockers are compared over 48 months.
  - Patients at risk: 77 (Beta-blockers) at 0 months.
  - Patients at risk: 33 (No beta-blockers) at 0 months.
  - Survival rates for both groups are compared with p < 0.0001.
The characteristic of refractory ascites is **repeated paracentesis**

Paracentesis further induces **arteriolar vasodilation** and results in **additional decrease in effective arterial blood volume**

Paracentesis has been shown to trigger a **paracentesis induced circulatory dysfunction syndrome (PICD)** characterized by **systemic vasodilation**

PICD is defined as an **increase in plasma renin concentration** of at least 50% one week after paracentesis
Paracentesis-induced circulatory dysfunction is associated with a decreased survival

- 289 patients with ascites treated by total paracentesis

\[ \text{PICD} \]

\[ \text{no PICD} \]

\[ p = 0.01 \]

β-blockers could contribute to PICD by blocking the increase in cardiac output normally observed

Ginès et al. *Gastroenterology* 1996
Beta-blocker therapy is associated with PICD

- 10 patients with cirrhosis and refractory ascites who had paracentesis at least twice in 1 month for 3 months
- Self-controlled cross-over design (i.e. each patient was his own control)

Sersté et al. *J Hepatol* 2011
Assessment of PICD in patients given beta-blockers

Sersté et al. *J Hepatol* 2011
Assessment of PICD after discontinuation of beta-blockers

Sersté et al. J Hepatol 2011
Assessment of PICD in cirrhotic patients with refractory ascites

The inability of the circulatory system to increase cardiac output in cirrhotic patients given NSBB increases the risk of PICD.

Sersté et al. J Hepatol 2011
Beta-blockers impact on survival in cirrhotics with spontaneous bacterial peritonitis (SBP)

- Retrospective analysis of 607 consecutive cirrhotic patients who had their first paracentesis - 182 developed SBP (first episode) during follow-up and among them 86 (47.3 %) received NSBB

- HR = 0.75 (0.58-0.97)  
  \[ p = 0.027 \]

- HR = 1.58 (1.10-2.27)  
  \[ p = 0.014 \]

Mandorfer et al. Gastroenterology 2014
Influence of NSBB treatment on hepatorenal syndrome (HRS) and grade C Acute kidney injury (AKI) development within 90 days after the first SBP diagnosis among cirrhotics with SBP. NSBBs increase the risks for AKI and HRS and reduce transplant-free survival.

Among cirrhotics with SBP, NSBBs increase the risks for AKI and HRS and reduce transplant-free survival.

Mandorfer et al. Gastroenterology 2014
NSBB treatment and risk of AKI in cirrhotic patients with severe alcoholic hepatitis

- 139 cirrhotic patients with severe alcoholic hepatitis histologically confirmed
  - 51 (46.8%) had NSBB

Sersté et al. Liver Int 2015
3) Which subset of cirrhotic patients could benefit the most from beta-blocker therapy?
Advanced cirrhosis (e.g. refractory ascites, SBP)

- Beta-blockers reduce survival due to negative impact on cardiac reserve, resulting in decreased perfusion to vital organs.

Decompensated cirrhosis (medium-large varices)

- Beta-blockers improve survival by reducing variceal bleeding and gut bacterial translocation.

Early cirrhosis

- Beta-blockers have no effect on survival and may increase adverse events.

Cardiac reserve

Sympathetic Nervous System activity

Renin-Angiotensin-Aldosterone System activity

Gut bacterial translocation

Appropriate timing for beta-blocker therapy: “The window hypothesis”

Conclusions

• Beta-blockers (nonselective) are part of the cornerstone of the medical management of primary and secondary prevention of variceal hemorrhage

• Beta-blockers are not indicated to prevent the development of varices in early cirrhosis

• Beta-blockers should be tapered and discontinued when patients develop end-stage cirrhosis with refractory ascites or SBP as decreased cardiac output results in decreased renal perfusion and increased risk for AKI, HRS and mortality
  - Beta-blockers should be promptly discontinued in the setting of either sepsis or HRS

Ge et al. J Hepatol 2014
Acknowledgments

- Dr. Thomas Sersté (UMC Saint Pierre, Brussels and C.U.B. Hôpital Erasme, Brussels, Belgium)

For your attention...
Additional research questions concerning beta-blocker therapy

- Appropriate dosing of NSBB in cirrhosis?
  - Previous studies used increasing doses until the heart rate was reduced by approximately 25%, with doses ranging from 20 to 180 mg given twice a day
  - ↓ hepatic venous pressure gradient (HVPG) to <12 mmHg or by >20% from baseline

- Further evaluation of newer-generation of NSBB
  - Studies on carvedilol are inconclusive

- Additional studies to evaluate the role and safety of beta-blockers in patients with advanced cirrhosis notably with refractory ascites and/or SBP are critically needed
  - Original RCTs excluded the subset of patients with refractory ascites!
Safety of NSBB in refractory ascites: A lively debate…

CORRESPONDENCE

The Deleterious Effects of Propranolol on Patients with Cirrhosis

Efe et al. Hepatology 2011

Beta-Blockers in Cirrhosis: Friend or Foe?

Galbois et al. Hepatology 2011

Selective β-blockers vs. placebo in patients with refractory ascites

Garcia-Pagán Nat Rev Gastroenterol Hepatol 2010

Effects of Beta-Blockers on Survival for Patients With Cirrhosis and Refractory Ascites

Lo. Hepatology 2011