A nonselective β-blocker did not prevent gastroesophageal varices in cirrhosis and portal hypertension

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.

Clinical impact ratings: Gastroenterology ★★★★★★☆

QUESTION

In patients with cirrhosis and portal hypertension, does a nonselective β-adrenergic blocker prevent gastroesophageal varices?

METHODS

Design: Randomized placebo-controlled trial.
Allocation: {Concealed}†.*
Blinding: Blinded {clinicians, patients, data collectors, outcome assessors, and data analysts}†.*
Follow-up period: Median 55 months (range 0 to 99 mo).
Setting: 4 centers in Barcelona, Spain; West Haven, Connecticut, and Boston, Massachusetts, USA; and London, United Kingdom.
Patients: 213 patients 18 to 74 years of age (mean 45 y, 59% men) with cirrhosis and portal hypertension (hepatic venous pressure gradient [HVPG] ≥ 6 mm Hg) and without gastroesophageal varices. Exclusion criteria included ascites, hepatocellular carcinoma, splenic or portal vein thrombosis, life-threatening concurrent illness, and primary biliary cirrhosis or sclerosing cholangitis.
Intervention: Oral timolol, median 11 mg (n = 108), or placebo, median 13 mg (n = 105) daily. The dose (range 1.25 to 80 mg) was based on prerandomization titration with timolol.
Outcomes: A composite endpoint of development of varices or variceal hemorrhage. Secondary outcomes were a composite of ascites, hepatic encephalopathy, liver transplantation, or death; treatment failure (primary endpoint, transplantation, or death); and adverse events.
Patient follow-up: 100% (intention-to-treat analysis).

MAIN RESULTS

The study drug was discontinued in 23% of patients in the timolol group and 20% in the placebo group. Timolol reduced heart rate, but not mean HVPG. Groups did not differ for development of varices or variceal hemorrhage (Table) or the proportions of patients who had large (≥ 5 mm) or small varices. In patients who did not reach a primary endpoint, groups did not differ for the secondary composite endpoint (Table) or for its individual components. The treatment failure rate was similar in the 2 groups (Table). Serious adverse events were more common in the timolol group (Table). Risk for varices was increased if baseline HVPG was ≥ 10 mm Hg.

CONCLUSION

In patients with cirrhosis of the liver and portal hypertension, a nonselective β-adrenergic blocker did not prevent development of gastroesophageal varices.

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*See Glossary.
†Information provided by author.

Timolol vs placebo to prevent varices in cirrhosis and portal hypertension at median 55 months‡

Outcomes	Timolol	Placebo	RRR (95% CI)	NNT
Varices or hemorrhage§	39% (42/108)	40% (42/105)	2.8% (–36 to 30)	Not significant
Ascites, hepatic encephalopathy, liver transplantation, or death	33% (22/66)	35% (22/63)	4.5% (–54 to 41)	Not significant
Treatment failure	55%	56%	2.8% (–24 to 24)	Not significant
			RRI (CI)	NNH (CI)
Serious adverse event	19%	5.7%	224% (41 to 661)	8 (5 to 24)

‡Abbreviations defined in Glossary; RRR, RRI, NNT, NNH, and CI calculated from data in article.
§Varices (36% vs 37%) and hemorrhage (2.8% vs 2.9%).

COMMENTARY

Esophageal and gastric collateral vessels form as a consequence of portal hypertension and, when large, can cause life-threatening variceal hemorrhage. Any strategy to prevent development of these collateral vessels seems to be a good idea. The pathophysiologic rationale for the study by Groszmann and colleagues is that β-blocking drugs reduced portal pressure in human studies and prevented collateral vessels in experimental animals (1). The study centers had a record of research in this area. The drug timolol was chosen as a potent nonselective β-blocking drug with greater affinity for both β_1- and β_2-receptors than propranolol or nadolol. Timolol was expected to reduce portal pressure as measured by HVPG, and the daily single dose was ideal to ensure compliance, which was greater than 80% in both groups. Thus, the rationale and methods would seem to ensure a successful outcome.

However, the results of this large and prolonged study were not as expected and certainly disappointing for the authors. Timolol reduced heart rate more than placebo, but only by 17%, to a mean of 62 beats/min. No significant differences in portal pressure, formation of varices, hemorrhage, ascites, encephalopathy, or death were observed between the 2 groups. It is important to note that patients receiving timolol also had more serious adverse effects.

The findings of this study show that formation of collateral vessels, although related to portal pressure, is not solved by β-blocking drugs. These drugs should not be offered to patients with cirrhosis and portal hypertension without varices. We should divert our research efforts to other mechanisms that initiate and perpetuate collateral vessel formation. Novel therapies designed for preventing cirrhosis rather than portal hypertension are more promising for the future.

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Reference

1. **Sarin SK, Groszmann RJ, Mosca PG, et al.** Propranolol ameliorates the development of portal-systemic shunting in a chronic murine schistosomiasis model of portal hypertension. J Clin Invest. 1991;87:1032-6.