Nadolol and isosorbide prevented recurrent variceal bleeding better than did endoscopic ligation in cirrhosis

Villanueva C, Miñana J, Ortiz J, et al. Endoscopic ligation compared with combined treatment with nadolol and isosorbide mononitrate to prevent recurrent variceal bleeding. N Engl J Med. 2001 Aug 30;345:647-55.

QUESTION

In patients with cirrhosis hospitalized for esophageal variceal bleeding, is treatment with nadolol and isosorbide mononitrate more effective than endoscopic ligation for preventing recurrent bleeding?

DESIGN

Randomized {allocation concealed*}†, {unblinded}†,* controlled trial with mean follow-up of 24 months.

SETTING

A hospital in Barcelona, Spain.

PATIENTS

144 patients (mean age 59 y, 63% men) who had cirrhosis, were hospitalized for esophageal variceal bleeding, and had emergency endoscopy. Exclusion criteria included < 18 years of age, poor hepatic function, advanced hepatocellular carcinoma, and life expectancy ≤ 6 months. All patients were included in the analysis with 9 patients censored at the time of the last visit.

INTERVENTION

72 patients were allocated to combined medication with nadolol, 80 mg orally once daily, adjusted over 5 days to reduce the resting heart rate by 25% (but not lower than 55 beats/min), and oral isosorbide mononitrate, progressively increased over 1 week from 20 mg once daily at bedtime to 40 mg twice/d

COMMENTARY

The study by Villanueva and colleagues provides new evidence for the greater effectiveness of a combined pharmacologic approach over endoscopic ligation to prevent recurrent esophageal variceal bleeding.

A major limitation of this study is the use of sclerotherapy or somatostatin, or both, rather than band ligation for endoscopic treatment of acute hemorrhage during the index or recurrent bleeds. A higher incidence of portal hypertensive gastropathy was also seen in the ligation group. Similar findings were reported by the same research group when comparing sclerotherapy with an identical regimen of nadolol and isosorbide mononitrate for prophylaxis of secondary bleeding (1). Most of the severe treatment-related complications in the ligation group were rebleeds related to esophageal ulcers (7 of 9), which raises the issue of whether the rebleeding (and complication rate) would have been lower if the authors had used banding for acute bleeding. Band ligation is currently considered the standard of care in the United States for endoscopic treatment of acute bleeding as well as for secondary prevention. The main limiting factors for aggressive pharmacologic portal pressure reduction are medication side effects and the lack of noninvasive methods to accurately measure portal venous pressures to monitor therapy effectiveness (2).

or to the maximal tolerated dose. 72 patients were allocated to endoscopic ligation with a single band with an overtube or a multiband device done after randomization, on day 7, and every 2 to 3 weeks until the varices were eradicated. Follow-up endoscopy was done at 3 months after eradication and every 6 months thereafter, and additional sessions of ligation were done, if required. In both groups, sclerotherapy or somatostatin, or both, were used for endoscopic control of acute hemorrhage during the index or recurrent bleeds.

MAIN OUTCOME MEASURES

Recurrent bleeding, complications, and mortality.

MAIN RESULTS

Analysis was by intention to treat and used Kaplan-Meier survival curves. The cumulative risk for recurrent bleeding was of borderline statistical significance between groups (P = 0.04) (Table). The cumulative risk for recurrent variceal bleeding was lower in the combined medication group than in the ligation group (Table). Fewer severe treatment-related complications occurred in the combined medication group than in the ligation group (3% vs 12%, P = 0.05), but groups did not differ for occurrence of overall complications (P = 0.71). Groups did not differ for cumulative risk for death (Table).

CONCLUSION

In patients with cirrhosis hospitalized for esophageal variceal bleeding, treatment with nadolol and isosorbide mononitrate prevented recurrent variceal bleeding more effectively than did endoscopic ligation.

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*See Glossary.

†Information provided by author.

Nadolol and isosorbide mononitrate (medication) vs endoscopic ligation for esophageal variceal bleeding in cirrhosis‡

Outcomes at mean 24 mo	Medication	Ligation	RRR (95% CI)	NNT (CI)
Risk for recurrent bleeding	33%	49%	23% (-2 to 52)	Borderline significance
Risk for recurrent variceal bleeding	28%	44%	33% (8 to 53)	7 (5 to 30)
Risk for death	32%	42%	15% (—13 to 38)	Not significant

‡Abbreviations defined in Glossary; RRR, NNT, and CI calculated from data provided by author.

The optimal evidence-based treatment algorithm favors initial medical treatment to reduce portal pressure and reserves endoscopic band ligation for treatment failures and patients intolerant of pharmacotherapy. Because direct measurements of portal pressures are not easily available, reduction of the resting pulse rate by 25% can be used as a surrogate end point. Early shunt surgery for well-compensated patients with good, long-term, transplant-free survival should also be considered. The effectiveness of medical treatment (β -blockers alone or with nitrates) combined with endoscopic band ligation warrants further investigation (3).

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References

- 1. Villanueva C, Balanzo J, Novella MT, et al. N Engl J Med. 1996;334: 1624-9.
- 2. D'Amico G, Pagliaro L, Bosch J. Semin Liver Dis. 1999;19:475-505.
- 3. Lo GH, Lai KH, Cheng JS, et al. Hepatology. 2000;32:461-5.