

# Endoscopic ligation was better than propranolol for prevention of bleeding from esophageal varices

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 Apr 1; 340:988-93.

## QUESTION

Is endoscopic ligation as efficacious and safe as propranolol therapy for primary prevention of bleeding from esophageal varices?

## DESIGN

Randomized, unblinded,\* controlled trial with 18-month follow-up.

## SETTING

India.

## PATIENTS

90 patients (mean age 42 y, 73% men) with portal hypertension who had never had bleeding from varices and had large (grade 3 or 4) varices but no history of hematemesis or melena. Patients were excluded if they were receiving antiviral therapy or if they had hepatoma or another tumor, severe cardiopulmonary or renal disease, heart failure, peripheral vascular disease, bradycardia, bronchial asthma, diabetes mellitus, prostatic hypertrophy, glaucoma, or a psychiatric disorder. Follow-up was 99%.

## INTERVENTION

46 patients were allocated to ligation, which was done every week until the varices were obliterated or reduced to a size of grade 1. If varices recurred and became grade 2 or larger, ligation was repeated. 44 patients were allocated to oral propranolol, 40 mg/d, with dose increments of 20 to 40 mg/d until a 25% decrease in baseline heart rate was achieved. Propranolol therapy was stopped if the patient had systolic blood pressure < 80 mm Hg, heart rate < 55 beats/min, or other serious side effects.

## MAIN OUTCOME MEASURES

Outcomes included variceal bleeding, need for blood transfusion, overall deaths, and deaths from variceal bleeding.

## MAIN RESULTS

Analysis was by intention to treat. At 18 months, the cumulative probability of variceal bleeding was lower in the ligation group than in the propranolol group (15% vs 43%,  $P = 0.04$ ). The hazard ratio for variceal bleeding in the propranolol group was 3.0 (95% CI 1.3 to 9.3); the

age-adjusted hazard ratio was 2.6 (CI 1.0 to 8.2). Fewer patients in the ligation group required blood transfusions (1 vs 7,  $P = 0.03$ ) than in the propranolol group. The groups did not differ for overall deaths (11% in each group,  $P = 0.77$ ) or bleeding-related deaths (7% vs 9%, [ $P = 0.67$ ]).

## CONCLUSION

Among patients with high-risk esophageal varices, endoscopic ligation was more efficacious than propranolol for primary prevention of bleeding.

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\*See Glossary.

† $P$  value calculated from data in article.

## COMMENTARY

This randomized trial by Sarin and colleagues showed that endoscopic sclerotherapy was superior to propranolol in the prevention of a first variceal hemorrhage in patients with portal hypertension who were at high risk for bleeding. Despite an impressive reduction in the hazard ratio (0.33), both groups had similar mortality rates.

Does this study invalidate use of pharmacotherapy in the prevention of first bleeding for all patients? I am convinced that, even for patients at high risk for bleeding, further studies are warranted before pharmacotherapy is abandoned in favor of endoscopic ligation. The reasons are 3-fold. First,  $\beta$ -blockade has withstood meta-analytical scrutiny in primary and secondary prevention of variceal bleeding (1). It is well known, however, that not all patients tolerate these drugs and not all respond to them. Therefore, although  $\beta$ -blockers may be considered the standard of care, they are not ideal. Further studies comparing banding ligation with more efficacious medical treatments, such as combining a  $\beta$ -blocker with isosorbide mononitrate or spironolactone, will be needed before

ligation should be adopted as the treatment of choice for primary prophylaxis. Second, the protective effect of these treatments in patients with cirrhosis, although in the same range, failed to reach statistical significance ( $P = 0.08$ ). This finding suggests that additional trials are required. Third, in these times, cost should also be considered when 2 treatment methods are being evaluated. It remains unclear whether the prevention of 8 bleeding episodes as shown in the present study justifies the higher cost of ligation therapy, particularly when the important outcome, survival, was not affected by the choice of treatment.

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## Reference

1. Bernard B, Lebec D, Mathurin P, Opolon P, Poynard T. Beta-adrenergic antagonists in the prevention of gastrointestinal rebleeding in patients with cirrhosis: a meta-analysis. *Hepatology.* 1997;25:63-70.