

immune escape phenomenon, facilitating endogenous virus persistence at low level in spite of HBV immunity.

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Is Banding Ligation for Primary Prevention of Variceal Bleeding as Effective as Beta-Blockers, and Is It Safe?

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To the Editor:

The randomized trial by Schepke et al.,¹ which showed that variceal banding ligation and propranolol were similarly effective for primary prophylaxis of variceal bleeding, is an important one. However, the study raises the issue of the effectiveness and safety of banding ligation in this setting. We feel that the safety of endoscopic ligation for primary prophylaxis is extremely important, as our own experience also raises this issue.²

Three trials have been published recently in this area.³⁻⁵ Two of these studies^{3,5} did not find significant differences between banding and propranolol, but one⁴ suggested that propranolol-treated patients with cirrhosis with high-risk esophageal varices had a significantly higher rate of bleeding from esophageal varices and greater cumulative mortality than those who had banding.

In this study⁴ the selection criteria excluded the very patients who may be more at risk of first bleeding—severe coagulopathy unresponsive to blood product transfusions, severe thrombocytopenia, gastric varices, documented hepatoma, portal or hepatic thrombosis, and large-volume or tense ascites; *i.e.*, the ones clinicians may wish to treat intensively. The impression given is that banding ligation is a totally

safe procedure in terms of iatrogenic bleeding. Jutabha et al.⁴ suggest that this is because the operators were all very experienced in banding ligation, but this is not supported by the literature—perhaps they were just lucky!

Thus, in the trial by Schepke et al trial bleeding from ligation occurred in 5 patients (6.7%), with 1 life-threatening and 2 fatal outcomes. This reflects our recently published experience.² A prophylactic therapy should be safe even if effective—*primum non nocere*.

Second, the authors should have evaluated their results in the context of others; they would have found themselves to be outliers. Indeed, the results were anomalous, as has also been felt to be the case in some previous studies.⁶ This is clear from a Forrest plot of a meta-analysis (Fig. 1). This should have led them to continue their study and not interrupt it early.

Moreover, it cannot be assumed that banding may be necessarily the best therapy for patients intolerant to beta-blockers.⁷ Although it is unlikely that varices in these patients are any different from those who tolerate beta-blockers, we experienced iatrogenic but not fatal bleeding with banding in our randomized study.²

We still need carefully conducted trials based on the population most seen in clinical practice; trials which do not have too much selection and which remember that patients may also bleed from portal hypertensive gastropathy. The published data by Schepke et al.¹ and our own experience² lead us to still consider nonselective beta-blockers

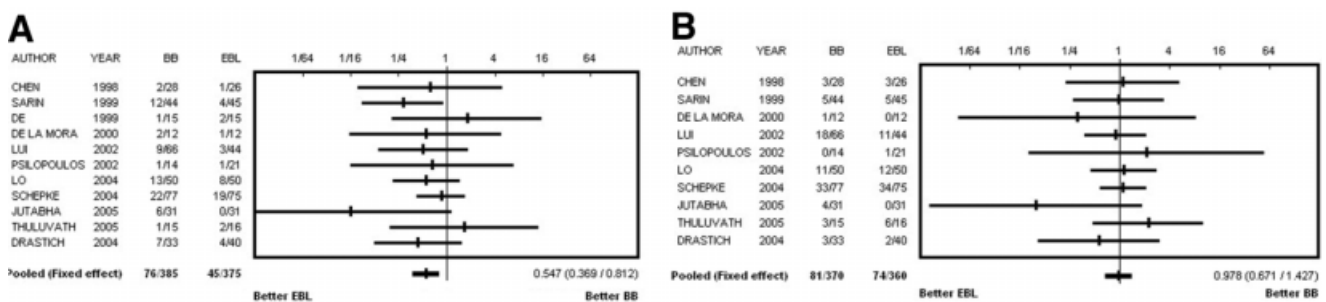


Fig. 1. (A) Meta-analysis plot of randomized trials of banding ligation of esophageal varices versus beta-blockers. Portal hypertensive bleeding. Data are expressed as OR (95% CI) in a log scale. (B) Meta-analysis plot of randomized trials of banding ligation of esophageal varices versus beta-blockers. Survival. Data are expressed as OR (95% CI) in a log scale. BB, beta-blockers; EBL, endoscopic band ligation.

as first-choice therapy for primary prophylaxis of portal hypertensive bleeding in cirrhosis, and not banding.⁴

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Outcomes, Effectiveness, Tolerability, and Direct Costs of Prophylactic Variceal Treatments

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To the Editor:

Thank you for allowing us to reply to a letter by Triantos et al. in this issue of *HEPATOLOGY*. Compared with rubber band ligation (RBL), the propranolol group in our study had significantly higher rates of (1) first esophageal varix hemorrhage, (2) failure (*e.g.*, first varix bleed and/or severe complications requiring stoppage of therapy), and (3) mortality.¹ The direct costs of medical therapy were not significantly different. Liver transplantation (OLT) rates were high in both treatment arms but did not account for the outcomes.² In our study, portal hypertensive gastropathy or banding ulcers did not cause severe bleeding in any patient. For a discussion of statistical issues, including an overlap of the confidence intervals of our results with other published trials, the reader is referred to our article.¹

Several specific issues in Triantos et al.'s letter merit clarification regarding primary prevention of first variceal hemorrhage. First, we agree that prophylactic therapies should be safe and effective. They also should be well tolerated. Propranolol is not very well tolerated, nor easy to use, nor very effective. Schepke et al.³ reported that 16% of patients had severe side effects, 5% had contraindications to its use, and only 52.8% achieved 25% reduction in resting heart rate as a surrogate for effectiveness. In other pharmacological studies, only about 60% of at-risk patients with cirrhosis on maximally tolerated doses of propranolol had true responses with reduction of their hepatic venous pressure gradients to 12 mm Hg or lower; therefore, 40% remained at high risk for variceal bleeding.⁴⁻⁶ These data do not support the premise that propranolol is very effective. Also, documenting hepatic venous pressure gradient response is very expensive and far exceeds the cost of RBL for varix eradication.⁷ Our position is that medical therapies that are more effective and safer than nonselective beta-blockers are needed as prophylactic therapies for high-risk patients. Meanwhile, propranolol should not be regarded as significantly superior to RBL with regard to safety, efficacy, tolerability, or cost.

Second, technical differences, study design, and luck may account for the lower complication rates with RBL in our trial¹ compared with

others,^{3,8} and these are important factors to understand. Some differences between our study and those of Schepke et al. and Triantos et al. are: (1) our use of proton pump inhibitors until complete varix obliteration; (2) the increasing time between RBL sessions to reduce complications and increase ulcer healing—4 to 5 weeks in our study¹ versus 1 week in the Schepke et al. study³ and 2 weeks in the Triantos et al. study⁸ (at 4 to 5 weeks banding ulcers were rare in our study); and (3) standardizing RBL techniques and varix obliteration among investigators before initiation of the study, which was part of our trial^{1,9} but was not discussed in the other two studies.^{3,8}

Third, there may be subgroup differences in response to these therapies.¹ Our study results are particularly relevant to nonalcoholic patients with cirrhosis but without prior variceal bleeding who are awaiting OLT and have high-risk varices. We recommend that physicians consider RBL as a treatment that is easier to apply, better tolerated, and potentially safer and more effective than propranolol in such patients.

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