

Living FRIendly Summaries of the Body of Evidence Using Epistemonikos (FRISBEE)

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Banding ligation or beta-blockers for primary prevention of variceal bleeding?

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Abstract

Variceal bleeding is one of the most serious complications of liver cirrhosis. Nonselective beta-blockers and endoscopic ligation are considered effective strategies for primary prevention of variceal bleeding, but there is no consensus about which alternative constitutes the best option. Searching in Epistemonikos database, which is maintained by screening 30 databases, we identified seven systematic reviews including 21 randomized controlled trials addressing the question of this article. We combined the evidence using meta-analysis and generated a summary of findings following the GRADE approach. We concluded variceal ligation probably decreases the risk of variceal bleeding and it is associated to less adverse effects when compared with nonselective beta blockers, although probably there is no difference in terms of mortality.

Problem

Gastro-esophageal varices are common in liver cirrhosis. The prevalence in stable cirrhosis varies between 30 and 40%, while in decompensated cirrhosis it reaches 60%. In patients with varices, the annual risk of bleeding is estimated at 30%, with a mortality rate ranging from 20 to 50% in each episode [1]. Nonselective beta-blockers are low-cost drugs that have proven effective in preventing variceal bleeding [2],[3], through reduction in porto-systemic pressure gradient, an important factor conditioning the rupture of varices. However, some patients do not tolerate them because of adverse effects. On the other hand, endoscopic ligation with elastic bands also prevents variceal bleeding in high risk patients [4],[5], but they have a higher cost, are more difficult to implement and have other associated risks. The aim of this article is to summarize the evidence comparing both prophylactic alternatives in patients with liver cirrhosis and high risk of variceal upper gastrointestinal bleeding.

Methods

We used Epistemonikos database, which is maintained by screening more than 30 databases, to identify systematic reviews and their included primary studies. With this information we generated a structured summary using a pre-established format, which includes key messages, a summary of the body of evidence (presented as an evidence matrix in Epistemonikos), meta-analysis of the total of studies, a summary of findings table following the GRADE approach and a table of other considerations for decision-making.

Key messages

- Primary prophylaxis with variceal ligation probably has little or no effect on the risk of mortality compared with nonselective beta blockers.
- Primary prophylaxis with variceal ligation probably reduces the risk of bleeding compared with nonselective beta-blockers and it is associated with fewer adverse effects.
- Variation on the decision about which intervention to use can be expected depending on patient preferences, available resources and availability of ligation.

About the body of evidence for this question

What is the evidence. See evidence matrix in Epistemonikos later	We found seven systematic reviews [1],[4],[5],[6],[7],[8],[9] including 21 randomized controlled trials reported in 26 references addressing the question of interest [10],[11],[12],[13],[14],[15],[16],[17],[18],[19],[20],[21],[22],[23],[24],[25],[26],[27],[28],[29],[30],[31],[32],[33],[34],[35].
What types of patients were included	All of the studies included patients with liver cirrhosis and presence of high-risk of bleeding varices, either by their large size (grade III or IV) or red spots.
What types of interventions were included	Eighteen trials [10],[12],[14],[15],[16],[17],[18],[19],[20],[21],[22],[25],[29],[30],[31],[32],[33],[34], used propranolol as beta-blocker, one trial [26] used nadolol, another [28] used carvedilol and one study[35] did not report the type of beta blocking agent used. Nine studies [12],[14],[19],[21],[25],[29],[30],[31],[34], conducted more than three ligation sessions and four studies [16],[17],[26],[28] performed fewer than three sessions. The other eight studies [10],[15],[18],[20],[22],[27],[32],[33] did not report the number of ligation sessions. Follow-up was longer than 1 year in all studies.
What types of outcomes were measured	The studies measured multiple outcomes, however those incorporated by most systematic reviews were: Overall mortality, bleeding related mortality, upper gastrointestinal bleeding from any cause and adverse effects.

Summary of findings

The information on the comparison between nonselective beta-blockers and ligation in primary prophylaxis of variceal bleeding is based on 21 randomized controlled trials involving 1659 patients. Twenty trials measured overall mortality (one study did not report this outcome [35]), 14 studies measured upper gastrointestinal bleeding from any cause and 10 studies evaluated adverse effects. The summary of findings is as follows:

- Primary prophylaxis with variceal ligation probably has little or no effect on the risk of mortality compared with nonselective beta blockers. The certainty of the evidence is moderate.
- Primary prophylaxis with variceal ligation probably reduces the risk of bleeding compared with nonselective beta-blockers. The certainty of the evidence is moderate.
- Primary prophylaxis with variceal ligation is associated to fewer adverse effects in comparison to nonselective beta-blockers. The certainty of the evidence is high.

Banding ligation versus nonselective beta-blockers for primary prevention of variceal bleeding				
Patients	Liver cirrhosis and presence of varices at high-risk of bleeding			
Intervention	Endoscopic variceal ligation			
Comparison	Nonselective beta-blockers			
Outcomes	Absolute effect*		Relative effect (95% CI)	Certainty of the evidence (GRADE)
	WITH Beta-blockers	WITH Variceal ligation		
	Difference: patients per 1000			
Mortality	236 per 1000	236 per 1000	RR 1.00 (0.84 to 1.19)	⊕⊕⊕○ ¹ Moderate
	Difference: 0 patients per 1000 (Margin of error: 38 less to 45 more)			
Upper gastrointestinal bleeding	202 per 1000	135 per 1000	RR 0.67 (0.54 to 0.84)	⊕⊕⊕○ ¹ Moderate
	Difference: 67 patients less per 1000 (Margin of error: 32 to 97 less)			
Severe adverse effects	More frequent with beta-blockers. The most severe adverse effects in endoscopic ligation group were bleeding secondary to procedure and esophageal perforation, but were very rare. The most severe adverse effects in beta-blockers group were symptomatic hypotension, bradycardia and dyspnea.		--	⊕⊕⊕⊕ ¹ High

RR= Risk ratio.
Margin of error = 95% confidence interval (CI).
GRADE: evidence grades of the GRADE Working Group (see later in this article).

* The risk **WITH BETA-BLOCKERS** is based on the risk in the control group of the trial. The risk **WITH VARICEAL LIGATION** (and its margin of error) is calculated from relative effect (and its margin of error)

¹ We downgraded the certainty of the evidence in one level because at least half of the studies have unclear risk of bias. We did not downgrade the certainty in the case of adverse effects since it is unlikely that this factor would introduce bias for this outcome.

About the certainty of the evidence (GRADE)*

⊕⊕⊕⊕

High: This research provides a very good indication of the likely effect. The likelihood that the effect will be substantially different† is low.

⊕⊕⊕○

Moderate: This research provides a good indication of the likely effect. The likelihood that the effect will be substantially different† is moderate

⊕⊕○○

Low: This research provides some indication of the likely effect. However, the likelihood that it will be substantially different† is high.

⊕○○○

Very low: This research does not provide a reliable indication of the likely effect. The likelihood that the effect will be substantially different† is very high.

*This concept is also called 'quality of the evidence' or 'confidence in effect estimates'.

† Substantially different = a large enough difference that it might affect a decision.

Other considerations for decision-making

To whom this evidence does and does not apply

- The information presented in this summary applies to adult patients with liver cirrhosis of any etiology and severity, presenting esophageal varices at high risk of bleeding.
 - This information does not apply to patients with low-risk esophageal varices or gastric varices.
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About the outcomes included in this summary

- The outcomes presented in the summary of findings table correspond to those critical for decision-making according to the opinion of the authors of this summary.
 - The outcome severe adverse effects was evaluated from three systematic reviews [5],[8],[9], which showed variability in the number of events reported in each primary study.
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Balance between benefits and risks, and certainty of the evidence

- Ligation probably does not reduce mortality compared with beta-blockers, but it might be associated with a lower risk of bleeding and less adverse effects, so it is the alternative with best benefit-risk balance.
 - While total adverse effects are more frequent with beta-blockers, it is important to consider the qualitative differences between them, especially severe ones. The most common side effects with endoscopic ligation were bleeding ulcers and procedural esophageal perforation. The other adverse effects were mild or moderate and generally transient, such as dysphagia, epigastric or chest pain. The main severe side effects with beta-blocker therapy were symptomatic hypotension, bradycardia and dyspnea. Other mild or moderate adverse effects frequently reported were dizziness, impotence and peripheral edema. In sum, even though adverse effects are lower with ligation, they are more severe than those observed with non-selective beta-blockers.
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What would patients and their doctors think about this intervention

- There may be differences in patient preferences for one or the other prophylactic therapy. For example, while some patients may prefer beta-blocker therapy, being less expensive and less invasive, other patients may be inclined to endoscopic therapy, because of the burden associated to daily consumption of a drug. Fear to severe adverse effects could also be a determining factor in the decision.
 - In situations where the cost or feasibility of ligation are an important limitation, a reasonable approach would be starting with beta blockers, reserving ligation for those with inability to maintain such therapy, either by considerations of the patient or adverse effects.
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Resource considerations

- Currently both strategies are widely available, however, band ligation has major limitations due to the need for a specialist to perform the procedure and the costs associated to the instruments.
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Differences between this summary and other sources

- The systematic reviews included in the analysis are consistent with each other. In all of them, as in our summary, it is concluded there are no differences in mortality between the two interventions, but there is a lower risk of upper gastrointestinal bleeding with variceal ligation.
 - Guidelines for primary prophylaxis of variceal hemorrhage partially agree with the conclusions of this summary. The BAVENO VI consensus [36] recommends for both medium and large esophageal varices, to select therapy based on available resources, expertise, patient preferences, contraindications and adverse effects profile. They add propranolol, nadolol or carvedilol are valid drug therapies, but suggesting carvedilol may be more effective in reducing portal pressure. Instead, the European guideline [37] recommends both therapies as primary prophylaxis, but indicates the first line of treatment is propranolol (and alternatively carvedilol or nadolol) and endoscopic therapy should be used only in case of contraindication, but always considering patient's preferences.
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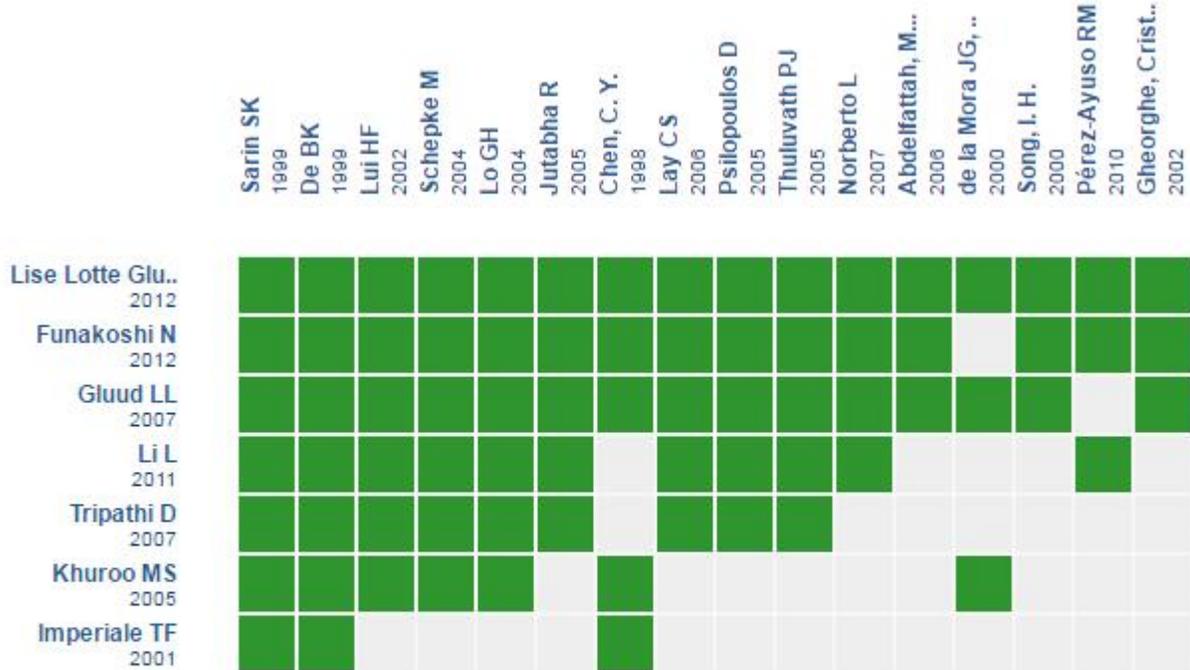
Could this evidence change in the future?

- The probability that future evidence change the conclusions of this summary is low due to the certainty of the evidence.
 - According to the records of the International Controlled Trials Registry Platform of the World Health Organization, there is at least one ongoing study [38] comparing endoscopic ligation versus propranolol, which could provide relevant information. However, given the certainty of the
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current evidence, there is a low probability that it will change the findings presented in this summary.

How we conducted this summary

Using automated and collaborative means, we compiled all the relevant evidence for the question of interest and we present it as a matrix of evidence.



Starting from any systematic review, Epistemonikos builds a matrix based on existing connections in the database. The author of the matrix can select relevant information for a specific health question (typically in PICO format) in order to display the information set for the question. The rows represent systematic reviews that share at least one primary study, and columns display the studies. The boxes in green correspond to studies included in the respective reviews.

Follow the link to access the **interactive version**: [Banding ligation versus beta-blockers for primary prevention of variceal bleeding.](#)

Notes

The upper portion of the matrix of evidence will display a warning of "new evidence" if new systematic reviews are published after the publication of this summary. Even though the project considers the periodical update of these summaries, users are invited to comment in *Medwave* or to contact the authors through email if they find new evidence and the summary should be updated earlier. After creating an account in Epistemonikos, users will be able to save the matrixes and to receive automated notifications any time new evidence potentially relevant for the question appears.

The details about the methods used to produce these summaries are described here <http://dx.doi.org/10.5867/medwave.2014.06.5997>.

Epistemonikos foundation is a non-for-profit organization aiming to bring information closer to health decision-makers with technology. Its main development is Epistemonikos database (www.epistemonikos.org). These summaries follow a rigorous process of internal peer review.

Conflicts of interest

The authors do not have relevant interests to declare.

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