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Should we add beta-blockers to band ligation for secondary prophylaxis of variceal bleeding?

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Abstract

Cirrhotic patients who have had an episode of bleeding from gastroesophageal varices are at high risk of rebleeding, despite treatment with endoscopic variceal ligation. Adding beta-blockers could reduce this risk, but it is associated with adverse effects. Searching in Epistemonikos database, which is maintained by screening multiple databases, we identified seven systematic reviews including 21 randomized controlled trials addressing the question of this article. We extracted data, combined the evidence using meta-analysis and generated a summary of findings following the GRADE approach. We concluded the addition of beta-blockers to endoscopic variceal ligation as secondary prophylaxis of variceal bleeding reduces the risk of rebleeding, but probably does not lead to any difference in terms of mortality. Even though it is associated to frequent adverse effects, these would be mild and generally do not lead to discontinuation of treatment.

Problem

Variceal bleeding in cirrhosis has a mortality risk between 20-50% per episode, as a consequence of hypovolemic shock or decompensation of underlying chronic liver damage [1]. Variceal rebleeding occurs in 60 to 70% of patients within the first two years after the first episode [2],[3],[4]. The standard strategy as secondary prophylaxis is eradication of varices with multiple sessions of endoscopic ligation. On the other hand, beta-blockers have proved to be better than placebo and randomized trials have shown there might be no difference in effectiveness when compared with endoscopic therapy [5],[6],[7],[8],[9],[10].

Endoscopic band ligation eradicates varices with high bleeding risk and beta-blockers reduce portal pressure, the main risk factor for variceal bleeding. However, it is not clear whether the combination of both therapies translates into a relevant clinical benefit when compared to endoscopic ligation alone.

Methods

We used Epistemonikos database, which is maintained by screening multiple 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

- The addition of beta-blockers to endoscopic variceal ligation as secondary prophylaxis of variceal hemorrhage, leads to a substantial reduction in the risk of rebleeding.
- The addition of beta-blockers to endoscopic variceal ligation as secondary prophylaxis of variceal hemorrhage might not reduce mortality, although the certainty of this evidence is low.
- The addition of beta-blockers would be associated to frequent but mild adverse effects, which generally do not lead to discontinuation of therapy, although the certainty of this evidence is low.

About the body of evidence for this question

What is the evidence. See evidence matrix in Epistemonikos later	We found seven [1],[2],[3],[4],[5],[11],[12] systematic reviews including three randomized controlled trials reported in four references addressing the question of interest [13],[14],[15],[16]. Two trials [17],[18] incorporated in most systematic reviews identified, were excluded from this summary because the treatment arm included isosorbide mononitrate.
What types of patients were included	All reviewed trials included patients who had already had a previous episode of variceal bleeding. Two trials [14],[15] included only cirrhotic patients. One trial [16] did not report whether all patients were cirrhotic. Only in one trial [14] most patients were Child B. Two trials [15],[16] did not report this data. In one trial [14], the most common cause of liver cirrhosis was alcohol. In another trial [15], the most common cause was viral and one trial [16] did not report this data.
What types of interventions were included	The interval between ligation sessions was less than three weeks in two trials [14],[15]. One trial [16] did not report this data. Propranolol was used in two trials [15],[16] and nadolol in one trial [14]. In all of the trials [14],[15],[16] the drug therapy was titrated to achieve a reduction of 25% of baseline heart rate. The follow-up time was greater than one year in one trial [14]. In two trials [15],[16] follow-up time was less than one year.
What types of outcomes were measured	The main outcomes were overall mortality and rebleeding in all of the systematic reviews identified. Four reviews [1], [2],[3],[12] included adverse effects in their analysis, but none of them reported the data of adverse effects of the trials included in this summary.

Summary of findings

The information on the effects of adding beta-blockers to endoscopic variceal ligation as secondary prophylaxis of variceal bleeding is based on three randomized trials involving 161 patients [14],[15],[16]. All of the trials reported mortality and rebleeding and only one reported adverse effects [14]. The summary of findings is as follows:

- The addition of beta-blockers to endoscopic variceal ligation as secondary prophylaxis of variceal hemorrhage leads to a substantial reduction in the risk of rebleeding. The certainty of the evidence is high.
- The addition of beta-blockers to endoscopic variceal ligation as secondary prophylaxis of variceal hemorrhage might not reduce mortality, although the certainty of this evidence is low.
- The addition of beta-blockers would be associated to frequent but mild adverse effects, which generally do not lead to discontinuation of therapy, although the certainty of this evidence is low.

Beta-blockers plus bland ligation in secondary prophylaxis of variceal hemorrhage				
Patients	Cirrhotic patients with a history of variceal bleeding			
Intervention	Endoscopic variceal ligation (EVL) plus beta-blocker (BB)			
Comparison	Endoscopic variceal ligation			
Outcomes	Absolute effect*		Relative effect (95% CI)	Certainty of the evidence (GRADE)
	WITH EVL alone	**WITH EVL plus BB**		
	Difference: patients per 1000			
Mortality	104 per 1000	83 per 1000	RR 0.8 (0.32 to 2.05)	⨁⨁⨁◯[1,2] Moderate
	Difference: 21 patients less per 1000 (Margin of error: 72 less to 109 more)			
Rebleeding	286 per 1000	97 per 1000	RR 0.34 (0.17 to 0.69)	⨁⨁⨁◯[1] High
	Difference: 189 patients less per 1000 (Margin of error: 89 to 237 less)			
Adverse effects	Only one trial [14] reported adverse effects in 14 of 43 patients in the combined therapy group, of which 3 discontinued treatment because of these.		--	⨁⨁⨁⨁[3] Low

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 EVL alone** is based on the risk in the control group of the trials. The risk **WITH EVL plus BB** (and its margin of error) is calculated from relative effect (and its margin of error)

[1] We did not downgrade the certainty of the evidence although there is high or not clear risk of bias in two of the three trials, because the trial that gives greater weight to meta-analysis has low risk of bias [14].
[2] We downgraded the certainty of the evidence in one level because the confidence interval is very wide.
[3] We downgraded the certainty of the evidence in two levels because of imprecision. The result is based on a limited number of cases of from a single trial.

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, who have already experienced an episode of variceal bleeding.
- It only applies to patients treated with endoscopic variceal ligation-based therapy and does not include sclerotherapy.
- This information does not apply to patients with liver cirrhosis with no history of variceal bleeding, or who have had an episode of upper gastrointestinal bleeding for any reason other than variceal.

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 article.

Balance between benefits and risks, and certainty of the evidence

- This is an intervention with a substantial benefit in terms of rebleeding and few adverse effects, which generally do not lead to discontinuation of therapy. While there is uncertainty about the latter, the balance between benefits and risks is favorable.
- There is uncertainty regarding the effect of beta-blockade on mortality in this scenario. On the one hand, it is expected that the decrease in rebleeding events would translate into a decrease in mortality risk resulting from the immediate complications of digestive hemorrhage. On the other hand, available evidence does not show a categorical decline in mortality. This situation can be explained by the fact that neither endoscopic therapy nor beta-blockade are involved in the progression of liver cirrhosis and the appearance of other serious complications of the disease, such as spontaneous bacterial peritonitis, refractory ascites, hepatorenal syndrome. On this regard, although combined acute therapy and prophylactic endoscopic therapy categorically reduce the risk of rebleeding, this does not necessarily translate into a decrease in mortality, since the variceal rebleeding episode would be a marker of poor prognosis and progression of liver failure, which ultimately explains long-term mortality.

What would patients and their doctors think about this intervention

- The vast majority of patients and doctors should lean in favor of combination therapy based on the evidence.
- While there is uncertainty about adverse effects, especially on their frequency and magnitude, probably these are not the main drivers for decision-making.

Resource considerations

- This is an inexpensive and widely available intervention, so the cost-benefit balance is very favorable.

Differences between this summary and other sources

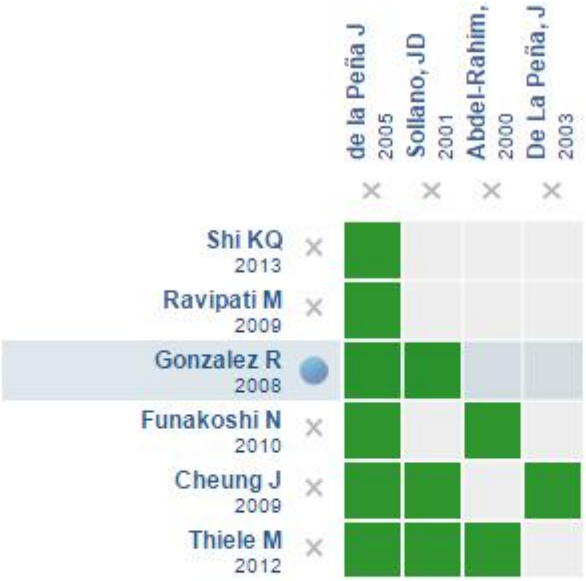
- The findings of our summary coincide with systematic reviews identified in relation to the risk of rebleeding.
- Clinical guidelines for secondary prophylaxis of variceal bleeding reach to similar conclusion to those reported in this summary. The consensus of BAVENO VI [19] recommended combination therapy as first-line treatment for secondary prophylaxis of variceal bleeding (either propranolol or nadolol). Carvedilol is not recommended by the absence of evidence to support it. On the other hand, the european guideline 2015 [20] provides exactly the same recommendations, except carvedilol is mentioned as an alternative to propranolol or nadolol.

Could this evidence change in the future?

- The probability that future evidence changes the conclusions presented in 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 trial [21] which would complete recruitment by 2018, with an estimate of 212 patients. This trial could add greater certainty, particularly with regard to adverse effects and the magnitude of benefit.

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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