

Living Friendly Summaries of the Body of Evidence using Epistemonikos (FRISBEE)

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Noradrenaline or terlipressin for hepatorenal syndrome?

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Abstract

Hepatorenal syndrome is a condition associated with very high mortality that may be reverted in some cases with vasoconstrictors. Terlipressin has generally been considered standard treatment, but noradrenaline has been postulated as alternative. Searching in Epistemonikos database, which is maintained by screening 30 databases, we identified six systematic reviews including four pertinent randomized controlled trials. We combined the evidence using meta-analysis and generated a summary of findings following the GRADE approach. We concluded noradrenaline and terlipressin probably have similar effects on reverting hepatorenal syndrome and decreasing mortality, but noradrenaline is associated with less adverse effects, and has lower costs.

Problem

Hepatorenal syndrome is a condition associated with very high mortality. It is caused by intense renal vasoconstriction consequence of systemic and portal hemodynamic disturbances, particularly splanchnic system vasodilation. Intravascular volume expansion and prolonged treatment with vasoconstrictors can revert kidney failure in some patients. Terlipressin improves renal function and decreases mortality, however it has frequent adverse effects, high cost, and it is not widely available. The use of alternative vasoconstrictors has been proposed, such as noradrenaline, which is widely available and has a lower cost.

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

- Noradrenaline and terlipressin probably have similar effects on reverting hepatorenal syndrome and decreasing mortality.
- Noradrenaline is associated with less adverse effects than terlipressin.
- Noradrenaline probably has a more favorable risk/benefit and cost/benefit ratio.

About the body of evidence for this question

What is the evidence. See evidence matrix in Epistemonikos later	We found six systematic reviews [1],[2],[3],[4],[5],[6] including four randomized controlled trials, reported in five references [7],[8],[9],[10],[11].
What types of patients were included	The studies included adults with advanced liver disease (Child Pugh C). One study [8] included patients with type 2 hepatorenal syndrome, one did not limit by hepatorenal type [7] and two studies included type 1 hepatorenal syndrome [9],[11]. MELD score ranged between 20 and 30 points in three studies [7],[9],[11] and more than 30 in one [8]. Average creatinine level ranged between 2 and 3 mg/dl in all of the studies.
What types of interventions were included	All studies compared terlipressin to noradrenaline. Noradrenaline dose ranged from 0.5 to 3 mg/hr. Terlipressin dose was 0.5 to 2 mg every 6 hours in three studies [8],[9],[11] and 1 to 2 mg every 4 hours in one [7].
What types of outcomes were measured	Mortality, renal function recovery and adverse events.

Summary of findings

The information on the effects of noradrenaline compared to terlipressin is based on four randomized trials including 154 patients. All studies reported the outcomes: mortality, hepatorenal syndrome reversal and adverse effects.

- Noradrenaline and terlipressin probably have similar effects on reverting hepatorenal syndrome. The certainty of the evidence is moderate.
- Noradrenaline and terlipressin probably have similar effects on decreasing mortality in hepatorenal syndrome. The certainty of the evidence is moderate.
- Noradrenaline is associated with less adverse effects than terlipressin. The certainty of the evidence is high.

Noradrenaline versus terlipressin for hepatorenal syndrome				
Patients	Hepatorenal syndrome			
Intervention	Noradrenaline			
Comparison	Terlipressin			
Outcomes	Absolute effect*		Relative effect (95% CI)	Certainty of the evidence (GRADE)
	WITH terlipressin	WITH noradrenaline		
	Difference: patients per 1000			
Mortality	500 per 1000	445 per 1000	RR 0.89 (0.68 to 1.17)	⊕⊕⊕ ¹ Moderate
	Difference: 55 patients less per 1000 (Margin of error: 160 less to 85 more)			
Hepatorenal syndrome reversal	590 per 1000	572 per 1000	RR 0.97 (0.76 to 1.23)	⊕⊕⊕ ¹ Moderate
	Difference: 18 patients less per 1000 (Margin of error: 142 less to 136 more)			
Adverse effects	282 per 1000	102 per 1000	RR 0.36 (0.15 to 0.83)	⊕⊕⊕⊕ ² High
	Difference: 180 patients less per 1000 (Margin of error: 48 to 240 less)			

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 terlipressin** is based on the risk in the control group of the trials. The risk **WITH noradrenaline** (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 of important risk of bias on the studies, mainly lack of blindness.
2 We did not downgrade the certainty of the evidence for risk of bias for the outcome adverse effects, considering the magnitude of the effect is large and it is unlikely that this aspect can modify it.

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

- Included studies evaluated patients with advanced cirrhosis with high Meld or Child-Pugh scores, with type 1 or 2 hepatorenal syndrome, so this evidence can be applied to the majority of patients presenting with this condition.
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About the outcomes included in this summary

- The outcomes included are those considered critical for decision-making by the authors of this summary: mortality, hepatorenal syndrome reversal and adverse effects. These coincide with those mentioned in the main guidelines [12],[13].
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Balance between benefits and risks, and certainty of the evidence

- Existing evidence shows equivalent benefit, but less adverse effects, so probably the benefit/risk ratio is favorable to noradrenaline.
 - However, it is important to mention the difference in adverse effects is not given by severe adverse effects, which are similar for both terlipressin and noradrenaline, but mainly by the higher frequency of abdominal pain and an increase in stool frequency.
-

What would patients and their doctors think about this intervention

- Terlipressin is considered standard treatment for hepatorenal syndrome, and consequently the main guidelines recommended it. Despite the existing evidence favoring noradrenaline there should be resistance from clinicians to adopt this therapy, at least while guidelines do not recommend it explicitly.
-

Resource considerations

- Noradrenaline has lower cost, so if we consider there is no difference in efficacy, it is probably a cost-effective intervention.
-

Differences between this summary and other sources

- The conclusions of this summary are in agreement with the more recent systematic review that includes all of the studies identified [4].
 - The main guidelines differ in their recommendations. The European guideline recommends terlipressin as first line therapy, but mentions noradrenaline as an alternative [12],[13]. The American guideline recommends using vasoactive agents, mainly octeotride or midodrine (terlipressin is not available in the United States), but recognizes the role of noradrenaline, limiting its use to critical care units.
-

Could this evidence change in the future?

- The probability of future evidence changing the conclusion of this summary is low, because of the certainty of the evidence.
 - There are no other completed or ongoing studies evaluating this question, at least according to the International Controlled Trials Registry Platform of World Health Organization.
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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.

	Ghosh S 2013	Singh V 2012	Singh, Virendra 2011	Sharma P 2008	Alessandria C 2007
Nassar Junior A... 2014					
Hiremath SB 2013					
Dobre M 2011					
Velez JC 2011					
Glud LL 2010					
Zhang ZF 2009					

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**: [Terlipressin versus noradrenaline for hepatorenal syndrome](#)

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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