Value of the hepatic venous pressure gradient to monitor drug therapy for portal hypertension: a meta-analysis
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CRD summary
The authors concluded that hepatic venous pressure gradient reduction could be used to monitor the haemodynamic response to drug therapy for treating variceal bleeding in patients with liver cirrhosis. Due to differences between studies, uncertainty over study validity and data extraction methods and use of observational cohorts with small numbers of patients, these conclusions should be treated with caution.

Authors' objectives
To assess whether target hepatic venous pressure gradient reduction can be used to monitor the haemodynamic response to drug therapy for prophylaxis of variceal bleeding in cirrhotic patients.

Searching
MEDLINE, EMBASE, The Cochrane Central Register of Controlled Trials and Cochrane Database of Systematic Reviews were searched to March 2006. In addition abstracts from the meetings of the American Gastroenterological Association, the American Association for the Study of Liver Disease, the European Association for the Study of Liver Disease and the British Society of Gastroenterology were hand searched by reviewing their annual meeting reports for the period 1999 to 2005. Search terms were reported. There was no restriction based on language. Reference lists of retrieved articles were searched for additional studies.

Study selection
Cohorts of cirrhotic patients with oesophageal varices, treated with β-blockers with or without organic nitrates for primary or secondary prophylaxis, were eligible for inclusion. Cohorts could be part of randomised controlled trials (RCTs), prospective non-randomised studies or retrospective studies. Studies had to measure the hepatic venous pressure gradient at baseline and post-drug treatment and report the target drug-induced reduction in pressure gradient.

The primary review outcomes were variceal bleeding (defined any episode of bleeding from varices over the follow-up period) and mortality resulting from liver-related death or the need for liver transplantation.

The included studies assessed treatment with β-blockers (propranolol or nadolol), with or without organic nitrates. Mean duration of follow-up ranged from 16 to 68 months where stated.

Three reviewers independently assessed studies for inclusion in the review. Any disagreements were resolved through consensus.

Assessment of study quality
Study quality was assessed on the basis of: source of the cohort of patients; whether the sample selection was explained; percentage of patients with hepatic venous pressure gradient not re-measured; definition of first or recurrent variceal bleeding; permanent recording of the tracings; and blind evaluation of the tracings by an investigator unaware of the clinical data. The maximum quality score was 10.

The authors did not state how the validity assessment was performed.

Data extraction
Pooled relative risk (RR) and 95% confidence intervals (CI) were calculated for each study.

Patients were classified according to the drug-induced hepatic venous pressure gradient (HVPG) change in the following groups: overall response (HVPG reduction to 12 mmHg or less or reduction by 20% or more from baseline); complete response (HVPG reduction to 12 mmHg or less); partial response (HVPG reduction 20% or greater from
baseline but final HVPG of 12 mmHg or more); and non-response (HVPG failed to reach either HVPG reduction to 12 mmHg or less or decrease of 20% or greater).

For each study, the number of patients in each HVPG response category, and the number of patients with bleeding or liver-related deaths in each of the HVPG response categories, was presented.

The authors did not state how the data were extracted for the review or how many reviewers performed the data extraction.

Methods of synthesis
Pooled relative risks and 95% confidence intervals (CIs) of variceal bleeding and death for overall, complete and partial hepatic venous pressure gradient response patients compared to the non-response patients were calculated using fixed-effect meta-analysis. A random-effects model was used where there was significant heterogeneity. The analysis was adjusted through the introduction of several predetermined trial-level covariates. Statistical heterogeneity was assessed using a $\chi^2$ test. The number needed to treat was also calculated with 95% CI. Meta-regression was used to examine the following: the influence of the percentage of non-evaluable patients; time to re-measurement of hepatic venous pressure gradient; baseline hepatic venous pressure gradient; length of follow-up; Child-Pugh score; and aetiology of cirrhosis. Analyses were repeated after excluding one outlying study and after including non-evaluable patients classified in the overall response group.

Results of the review
Ten cohorts were included (n=595 patients) with hepatic venous pressure gradient measures at baseline and follow-up who were included in analyses). These cohorts came from two RCTs, five prospective non-randomised studies, and three cohorts representing some patients who were originally part of RCTs. Quality scores were between 4 and 8, with eight studies scoring between 6 and 8.

Primary and secondary prophylaxis:

The risk of variceal bleeding was significantly lower in patients with a hepatic venous pressure gradient (HVPG) reduction (classified as overall, complete or partial) compared with patients without a HVPG response.

For overall HVPG response patients, the relative risk of bleeding was 0.27 (95% CI: 0.14 to 0.52) with significant heterogeneity ($p=0.011$) and the number needed to treat was 3 (95% CI: 2 to 5). In complete HVPG response patients, the relative risk of bleeding was 0.48 (95% CI: 0.28 to 0.81) without heterogeneity. In partial HVPG response patients the relative risk of bleeding was 0.41 (95% CI: 0.20 to 0.81) with heterogeneity ($p=0.007$).

Exclusion of an outlying study that reported the longest interval to re-measurement, and had the lowest quality score, yielded a significantly lower risk of bleeding, without heterogeneity. The recalculated relative risk of bleeding was 0.23 (95% CI: 0.15 to 0.36) for overall HVPG response patients, 0.27 (95% CI: 0.13 to 0.56) for complete HVPG response patients, and 0.33 (95% CI: 0.21 to 0.51) for partial HVPG response patients.

The relative risk of liver-related mortality was significantly lower in overall HVPG response patients (12% versus 26%, relative risk 0.58, 95% CI: 0.37, 0.91) compared to HVPG non-response patients, without heterogeneity. The number needed to treat was 6 (95% CI: 4 to 11). The relative risk of any death or liver transplantation was significantly lower for overall HVPG response patients compared to HVPG non-response patients at 0.71 (95% CI: 0.49 to 1.0), without heterogeneity.

Primary prophylaxis (four cohorts, n=185 patients):

The relative risk of variceal bleeding was significantly lower in overall (0.24, 95% CI: 0.10 to 0.56) and partial (0.30, 95% CI 0.12 to 0.77) HVGP response patients compared with HVPG non-response patients, without heterogeneity. The number needed to treat for both overall and partial HVPG response patients was 4 (95% CI: 2 to 8).

Secondary prophylaxis (six studies, n=363 patients)
Overall HVPG response patients showed a significantly lower variceal bleeding risk than HVPG non-response patients (16% versus 46%, relative risk 0.35, 95% CI 0.16 to 0.80), with significant heterogeneity (p=0.006). The relative risk of bleeding was non-significantly lower in partial HVPG response patients (0.52, 95% CI 0.22 to 1.22), with significant heterogeneity (p=0.003). Exclusion of the study reporting the longest interval to re-measurement yielded a relative risk of bleeding of 0.38 (95% CI: 0.23 to 0.62). The number needed to treat was 3 (95% CI: 2 to 4).

Authors’ conclusions
Findings supported the validity of hepatic venous pressure gradient endpoints to monitor drug therapy efficacy for variceal bleeding prophylaxis.

CRD commentary
This review addressed a clear question and undertook a comprehensive search for studies, with no restriction based on language or study design. The authors made appropriate attempts to minimise bias in the study selection, but it was unclear how many of the authors were involved in the quality assessment and data extraction. This raised the potential for reviewer error and bias. An assessment of the methodological quality of the included studies was undertaken and incorporated into the discussion of results. The quality of many of the included studies was low. Appropriate methods were used for the meta-analysis. Heterogeneity was assessed. Attempts were made to examine potential sources of heterogeneity and differences between studies were discussed. In light of the differences between studies, uncertainty over study validity and data extraction methods and use of small numbers of patients from observational cohorts, these conclusions should be treated with caution.

Implications of the review for practice and research
Practice: The authors stated that hepatic venous pressure gradient monitoring should be incorporated in the armamentarium used to manage patients with cirrhosis. Repeated hepatic venous pressure gradient measurements should be the gold standard for the assessment of new therapies and non-invasive methods for the treatment or evaluation of portal hypertension.

Research: The authors did not state any implications for research.

Funding
Ministerio de Educacion y Ciencia, grant number BFU 2006-09280/BFI; Ministerio de Sanidad y Consumo, Instituto de Salud Carlos III, grant number PI051871; Fundacion Mutua Madrilena.

Bibliographic details

PubMedID
17391317

DOI
10.1111/j.1572-0241.2007.01191.x

Original Paper URL
http://www.nature.com/ajg/journal/v102/n5/abs/ajg2007206a.html

Indexing Status
Subject indexing assigned by NLM

MeSH
Antihypertensive Agents /therapeutic use; Chi-Square Distribution; Esophageal and Gastric Varices /etiology /physiopathology /prevention & control; Gastrointestinal Hemorrhage /etiology /physiopathology /prevention & control;
Hepatic Veins /physiopathology; Humans; Hypertension, Portal /drug therapy /physiopathology; Portal Pressure /drug effects; Regression Analysis; Venous Pressure /drug effects

**AccessionNumber**

12007001807

**Date bibliographic record published**

07/01/2008

**Date abstract record published**

22/07/2009

**Record Status**

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