Measuring the hemodynamic response to primary pharmacoprophylaxis of variceal bleeding: a cost-effectiveness analysis
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Record Status
This is a critical abstract of an economic evaluation that meets the criteria for inclusion on NHS EED. Each abstract contains a brief summary of the methods, the results and conclusions followed by a detailed critical assessment on the reliability of the study and the conclusions drawn.

Health technology
The routine haemodynamic monitoring (HDM) of primary pharmacoprophylaxis of oesophageal variceal bleeding (OVB) in patients with cirrhosis was examined. HDM required percutaneous catheterisation of the hepatic vein and measurement of the hepatic venous pressure gradient. HDM was performed before and during the administration of pharmacoprophylaxis, to assess haemodynamic response.

Type of intervention
Primary prevention.

Economic study type
Cost-effectiveness analysis.

Study population
The study population comprised a hypothetical cohort of patients with cirrhosis, portal hypertension, and medium to large oesophageal varices, who were candidates for primary prophylaxis with nonselective beta-blocker therapy. The authors noted that the current analysis applied best to patients with Child class A or B cirrhosis.

Setting
The setting was a hospital. The economic study was conducted in the USA.

Dates to which data relate
The effectiveness evidence and the resource use data were derived from studies published between 1986 and 2001. The price year was 2001.

Source of effectiveness data
The effectiveness evidence was derived from a review of completed studies and authors' assumptions.

Modelling
A decision model based on Markov cycles was constructed to compare the clinical and economic outcomes of HDM versus no monitoring. In the no monitoring branch, pharmacoprophylaxis-tolerant patients received beta-blocker therapy while those intolerant to pharmacoprophylaxis underwent endoscopic variceal ligation (EVL). In the HDM arm, patients who did not tolerate pharmacoprophylaxis underwent EVL while the others received standard beta-blocker therapy. In monitored patients who did not respond to beta-blocker therapy alone, the model considered two different paths. More specifically, the addition of nitrates or EVL. Again, those who did not tolerate therapy underwent EVL. The structure of the tree and the Markov states were reported graphically in the paper. The length of the Markov cycles was one month and the time horizon of the model was 5 years. The structure of the tree did not consider
noncompliance, the use of liver transplantation, non-variceal causes of bleeding, or complications from ligation, transjugular intrahepatic portosystemic shunt (TIPS) and HDM.

Outcomes assessed in the review
The outcomes assessed from the literature were the probabilities of the following:

tolerating beta-blocker therapy;

a haemodynamic response to beta-blocker therapy;

a haemodynamic response to beta-blocker therapy and nitrates (when tolerated);

a 5-year risk of bleeding;

TIPS for refractory bleeding;

a risk of death from an episode of bleeding;

a 2-year risk of death from other (non-bleeding) causes;

a relative risk (RR) of bleeding given a haemodynamic response;

a RR of bleeding given no haemodynamic response; and

a RR of bleeding given prophylactic ligation.

Some assumptions were also made on the basis of the literature.

Study designs and other criteria for inclusion in the review
A formal review of the literature was not undertaken and the design of the primary studies was not reported.

Sources searched to identify primary studies
Not stated.

Criteria used to ensure the validity of primary studies
Not stated.

Methods used to judge relevance and validity, and for extracting data
Not stated.

Number of primary studies included
Fourteen primary studies were used to provide the probability data.

Methods of combining primary studies
Not stated.

Investigation of differences between primary studies
Not stated.
Results of the review
The estimated probabilities were:

- 0.85 (range: 0.6 - 1) for tolerating beta-blocker therapy;
- 0.45 (range: 0.2 - 0.6) for a haemodynamic response to beta-blocker therapy;
- 0.90 (range: 0.6 - 1) for a haemodynamic response to beta-blocker therapy and nitrates (when tolerated);
- 0.50 (range: 0.3 - 0.6) for a 5-year risk of bleeding;
- 0.10 (range: 0 - 0.5) for TIPS for refractory bleeding;
- 0.15 (range: 0.1 - 0.5) for a risk of death from an episode of bleeding;
- 0.33 (range: 0.25 - 0.4) for a 2-year risk of death from other (non-bleeding) causes;
- 0.20 (range: 0.1 - 0.5) for a RR of bleeding given a haemodynamic response;
- 0.90 (range: 0.8 - 1.2) for a RR of bleeding given no haemodynamic response; and
- 0.35 (range: 0.25 - 0.5) for a RR of bleeding given prophylactic ligation.

On the basis of published evidence, it was assumed that:

- ligation required a mean of 3.3 sessions to eradicate varices, with surveillance endoscopy every 6 months thereafter to detect and ligate recurrent varices;
- the risk of bleeding during a cycle after an episode of variceal bleeding was 10 times the baseline risk, and was twice the baseline risk thereafter for those not receiving TIPS; and
- complications from monitoring were negligible.

Methods used to derive estimates of effectiveness
The authors made some assumptions that were used in the decision model.

Estimates of effectiveness and key assumptions
It was assumed that intolerance of treatment or non-response occurred within the first month. In addition, ligation was used as initial treatment for bleeding episodes, with TIPS reserved for rescue treatment. Multiyear risks of bleeding or death were assumed to be linear over time and were converted to cycle probabilities.

Measure of benefits used in the economic analysis
The summary benefit measure used was the life-years saved. These were obtained from the decision model and were discounted at an annual rate of 3%. Secondary model outputs were the proportions of bleeders, TIPS and deaths.

Direct costs
A discount rate of 3% was applied since the costs were incurred during a 5-year period. The unit costs were not presented separately from the quantities of resources used. The costs were not broken down. The health services included in the economic evaluation were HDM sessions, beta-blocker therapy, nitrates, ligation sessions, endoscopic surveillance, episodes of bleeding, and TIPS placement and follow-up. The cost/resource boundary of the health care system was adopted. Resource use was estimated using probability values derived from the literature, while the costs...
came from Medicare rates and published data. All the costs were presented in 2001 values.

**Statistical analysis of costs**
The costs were treated deterministically in the base-case.

**Indirect Costs**
The indirect costs were not considered.

**Currency**
US dollars ($).

**Sensitivity analysis**
Sensitivity analyses were conducted to address the issue of variability in the data. All the model inputs, including the discount rate, were varied in a one-way sensitivity analysis. This permitted the more clinically relevant or sensitive variables to be identified. These variables were then varied in the two-way sensitivity analysis. Probabilistic sensitivity analyses were also conducted in a Monte Carlo simulation using 10,000 iterations. The ranges of values used were derived from the literature or Medicare rates.

**Estimated benefits used in the economic analysis**
The estimated discounted life-years were 2.864 with no monitoring, 2.922 with HDM plus nitrates, and 2.908 with HDM plus ligation.

The estimated proportions of bleeders, TIPS and deaths were:

- 20.6% (bleeders), 2.26% (TIPS) and 66.8% (deaths), respectively, with no monitoring:
- 9.4% (bleeders), 0.91% (TIPS) and 64.9% (deaths), respectively, with HDM plus nitrates; and
- 11.7% (bleeders), 1.16% (TIPS) and 65.2% (deaths), respectively, with HDM plus ligation.

This meant that, in a hypothetical cohort of 1,000 eligible patients in a 5-year timeframe, HDM plus nitrates would prevent 112 episodes of variceal bleeding, 14 TIPS and 18 deaths compared with no monitoring.

In terms of the number-needed-to-treat, 9 patients would have to undergo HDM to avoid one initial episode of variceal bleeding.

**Cost results**
The estimated discounted costs were $6,063 with no monitoring, $5,915 with HDM plus nitrates, and $6,312 with HDM plus ligation.

**Synthesis of costs and benefits**
Incremental cost-effectiveness ratios (ICERs) were calculated to combine the costs and benefits of the strategies under evaluation. HDM with nitrates dominated both no HDM and HDM with ligation, which were both more expensive and less effective.

The ICER of HDM with ligation relative to no HDM was $5,659. The estimated ICER was not sensitive to variations in most of the model inputs varied in the sensitivity analysis. However, some striking results were observed.

The benchmark value of $50,000 per life-year gained with HDM was exceeded in the following situations:
when the time horizon was shorter than 22 months (but HDM plus nitrate strategy was cost-saving after 49 months);
when the probability of a haemodynamic response was greater than 0.87; or
when the cost of a session of HDM was higher than $1,700 (3.5 times the base-case value).

The probabilistic sensitivity analysis suggested that:
when comparing HDM plus nitrate with no HDM, monitoring was more effective in 100% of the cases and less costly in 57% of the cases;
when comparing HDM alone with no HDM, monitoring was more effective in 59% of the cases and less expensive in 43% of the cases; and
when comparing monitoring with nitrates and monitoring alone, HDM plus nitrate was more effective in 52% of the cases and less costly in 64% of the cases.

Authors' conclusions
In cirrhotic patients with medium to large oesophageal varices, haemodynamic monitoring (HDM) was a cost-effective strategy that led to cost-savings under specific conditions. The results were sensitive to the timeframe of the analysis.

CRD COMMENTARY - Selection of comparators
Several strategies for the management of patients receiving prophylaxis for OVB were considered (HDM with either nitrates or ligation). All of them appear to have been appropriate for reflecting the actual treatment patterns of the population considered in the study. The rationale for the choice of the basic comparator, no monitoring, was clear since it represented the current standard. You should decide whether these are valid comparators in your own setting.

Validity of estimate of measure of effectiveness
The effectiveness evidence was derived from the literature. However, a formal review was not conducted and information on the design of the primary studies was not reported. Therefore, it was difficult to evaluate the validity of the sources used. The authors stated that some conservative assumptions were made which favoured the comparison strategy. Most of the probability estimates and assumptions were then varied in the sensitivity analyses, which, to some extent, enhanced the internal validity. The authors noted that their findings might not apply to patients with small varices or to those with Child class C cirrhosis, as most of the patient series in the primary studies referred to patients with Child class A and B cirrhosis.

Validity of estimate of measure of benefit
The use of life-years as the summary benefit measure appears to have been appropriate, both for assessing the impact of the intervention on the patients' health and for making comparisons with the benefits of other health care interventions. Discounting was applied and then varied in the sensitivity analysis.

Validity of estimate of costs
The authors explicitly reported the perspective adopted in the study. It appears that all the relevant categories of costs have been included in the analysis. However, the costs were not broken down, which would hinder the replication of the study in other settings. The cost data were derived from Medicare rates and published data. The authors performed several sensitivity analyses to address uncertainty in the cost estimates. The costs were presented as point estimates in the base-case, but probabilistic distributions were then attributed to both the costs and quantities of resources used to carry out stochastic sensitivity analyses. The price year was given, thus enabling reflation exercises.

Other issues
The authors compared their findings with those derived from a published study that used a management strategy with HDM, which was comparable to that investigated in the current study. The issue of the generalisability of the study results was not explicitly addressed. However, the external validity of the analysis was enhanced by the use of extensive sensitivity analyses, the results of which were reported in detail. The authors justified their choice of a modelling approach on the grounds that there was a lack of valid randomised trials in large series showing the cost-effectiveness of HDM. Some limitations of the analysis, mainly related to the structure of the decision tree, were also discussed.

**Implications of the study**
The authors noted that, in future analyses, patient values for different health states could be incorporated into the decision model. Further research, to corroborate the findings of the current study, should be based on a prospective randomised trial.

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