A cost-effectiveness study of hepatic venous pressure gradient measurement in the secondary prevention of variceal bleeding

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ABSTRACT

Objective: variceal rebleeding is common following a first episode of hemorrhage in cirrhotic patients. The objective of this study was to determine the cost-effectiveness of monitoring hepatic venous pressure gradient (HVPG) to guide secondary prophylaxis.

Methods: we created a Markov decision model to calculate cost-effectiveness for two strategies: Group 1: HVPG monitoring to decide treatment – when portal pressure was reduced by at least 20 percent or HVPG was less than 12 mmHg after beta-blocker administration, patients received beta-blockers; when portal pressure did not meet these criteria therapy was endoscopic band ligation. Group 2: in this group there was no monitoring of HVPG. Patients with large varices received treatment with beta-blockers combined with EBL; patients with small varices received beta-blockers plus isosorbide mononitrate.

Results: there was no recurrent variceal bleeding in group 1 for good responders, and for 17% of poor responders. In group 2 a 25% rebleeding rate was detected in patients with small varices and 13% for those with big varices. Overall cost in group 1 was 14,100.49 euros, and 14,677.16 in group 2.

Conclusions: HVPG measurement is cost-effective for the secondary prophylaxis of variceal bleeding.

Key words: Variceal bleeding. Hemodynamic study. Beta-blockers.

INTRODUCTION

Upper gastrointestinal (GI) bleeding secondary to variceal bleeding from esophagogastric varices is one of the major complications of portal hypertension. The latter
occurs in 25-35% of cirrhotic patients and causes 80-90% of bleeding events in these patients. The mortality rate (for each event) is around 20%, and almost 60% of patients surviving a first event will have recurrent hemorrhage without prophylaxis (3). In all, 30-40% of recurrence cases take place within six weeks after the initial event. Survival rates decrease to 50% (3) one year after the first hemorrhage.

The bleeding risk is determined by several factors. A major one is a hepatic venous pressure gradient (HVPG) increase determined by the difference in pressures between the portal territory and suprarepatic veins. HVPG is higher in cirrhotic patients due to blocked intersinusoidal communications to loss of structure in the hepatic parenchyma. It has been observed that HVPG should be higher than 12 mmHg for bleeding to occur, so a lower gradient may avoid the risk for recurrent hemorrhage. In view of high mortality and recurrence rates bleeding prophylaxis is indicated. The current methods available to avoid rebleeding include pharmacological measures that may be combined with endoscopic techniques.

Non-cardioselective beta-blockers such as propranolol and nadolol have proven effective for hemorrhage prevention (5), and their association with isosorbide-5-mononitrate obtains a higher reduction in portal pressure. Rubber band ligation (RBL) is the endoscopic treatment of choice nowadays, as it significantly reduces recurrent hemorrhage (7). Although a combination of both treatments (pharmacological and endoscopic) works better to reduce bleeding risks, the usefulness of combined treatment has not been well established yet.

Treatment choice is based on endoscopic criteria, so patients presenting with small varices (grade I-II) underwent pharmacological treatment and patients with large varices (grade III-IV) underwent RBL. However, performing a hemodynamic study to evaluate HVPG response prior to and after propranolol administration permits to distinguish good responders from non-responders. Thus, treatment is optimized and unnecessary drugs are not used with non-responders. For this reason, HVPG response to pharmacological treatment is recommended as guidance on the prophylactic treatment (9). Information on the cost-effectiveness of this procedure is not available in Spain.

**OBJECTIVE**

The aim of this study was to determine cost-effectiveness for a hemodynamic study prior to the prophylactic treatment of variceal bleeding in cirrhotic patients.

**MATERIAL AND METHODS**

Two groups of patients were considered in this study. Group I (Table I): cirrhotic patients admitted to our hospital (Hospital General Universitario de Alicante) due to a variceal bleeding event. All members of group I underwent a hemodynamic study prior to prophylactic treatment choice in order to assess whether they were good responders or non-responders to propranolol. The study was performed after treatment with somatostatin was discontinued, around five days after admission. The technique, performed under local anesthetic and septic conditions, consists of the introduction of a catheter-balloon through the right internal jugular, femoral, or anterior cubital vein until the hepatic vein is reached; once there the free hepatic venous pressure is recorded with the flat balloon, and then the wedged hepatic venous pressure is recorded after balloon inflation. HVPG is determined by the difference between both pressures. A dosage of 0.15 mg/kg intravenous propranolol is provided after a baseline recording; subsequently, HVPG is determined as mentioned above. Patients are considered “good responders” when HVPG shows a 20% decrease or is lower than 12 mmHg, and are then treated with non-cardioselective betablockers (11). “Non-responders” undergo RBL until varices are eradicated according to the design described by De Madaria et al. (12).

**Cost-effectiveness analysis**

**Strategies and model**

A Markov decision model was applied to assess cost-effectiveness in both clinical strategies in the treatment of upper variceal bleeding in cirrhotic pa-

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**Table I. Group 1. Epidemiological variables**

<table>
<thead>
<tr>
<th>Variable</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>56.6 ± 9.2</td>
</tr>
<tr>
<td>Sex (M/F)</td>
<td>24/12</td>
</tr>
<tr>
<td>Alcoholic/non-alcoholic cirrhosis etiology</td>
<td>18/18</td>
</tr>
<tr>
<td>Child-Pugh</td>
<td>8.1 ± 2</td>
</tr>
<tr>
<td>Ascites</td>
<td>17</td>
</tr>
<tr>
<td>Total bilirubin (mg/dl)</td>
<td>1.9 (1-3.4)</td>
</tr>
<tr>
<td>Quick index (%)</td>
<td>62.6 ± 15.9</td>
</tr>
<tr>
<td>Blood plates</td>
<td>98,022 ± 49,501</td>
</tr>
<tr>
<td>Variceal size I/III-IV</td>
<td>13/23</td>
</tr>
<tr>
<td>Esophagogastric varices</td>
<td>9</td>
</tr>
<tr>
<td>Monitoring</td>
<td>14.9 ± 9.3</td>
</tr>
</tbody>
</table>
tients. HVPG or varice size were considered decisive of the therapeutic strategy (Fig. 1). At the beginning of the tree, cirrhotic patients are supposed to present with upper GI bleeding due to esophageal varices without any other comorbidities. Patients may undergo a hemodynamic study to determine HVPG, and are classified as good responders and non-responders that might suffer from recurrent bleeding. Probability rates in this branch of the tree are the findings from a prospective cohort study performed in our hospital (12). Patients who underwent no hemodynamic study had a therapeutic/diagnostic endoscopy, and were classified according to the size of esophageal varices. They may suffer from recurrent bleeding subsequently. Probability rates in this branch come from literature data (13). It was assumed in the model that every patient included in the hemodynamic study were classified according to the size of varices or vice versa. For all cases it was considered that recurrence was due to new upper GI bleeding from esophageal varices, all patients were classified, and dropout rate was similar in both branches. We chose a one-year period with one recurrence event per patient at most.

**Costs**

Costs were obtained from the health costs database at the hospital’s “Servicio de Información Económica” for year 2004, coinciding with the inclusion of patients in the prospective cohort study performed in our hospital (12). Costs considered were: gastroscopy costs, hemodynamic study, days of stay in the Digestive Bleeding Unit, endoscopic treatment with rubber and medicines (market cost in Spain in 2004). The same stay in the Digestive Bleeding Unit was assumed for all patients (average stay was 5 days). All patients underwent a diagnostic endoscopy at the beginning of the study, and 25% also had a therapeutic procedure (rubber band placement). For patients treated with rubber bands the treatment consisted of 3 sessions including the cost of gastroscopy and a rubber band kit each. A dose of propranolol of 120 mg/day was assumed to calculate costs. Other costs derived from the medical care assistance process (comorbidities, visit to consulting room, etc.) were assumed to be the same for both groups.

Indirect and intangible costs were not considered. All costs were calculated in euros. No discount rate was considered since patients and costs occurred simultaneously. All analyses were performed on the basis of the Spanish National Health System. Costs are summarized in table II. Incremental cost was calculated as the difference between the strategy including a hemodynamic study and the strategy not including it.

**Table II. Unitary costs**

<table>
<thead>
<tr>
<th>Unitary cost</th>
<th>Euros</th>
</tr>
</thead>
<tbody>
<tr>
<td>Day of stay in the Digestive Bleeding Unit</td>
<td>2,234,12 €</td>
</tr>
<tr>
<td>Gastroscopy (1 rubber band kit in 25% of diagnostic gastroscopies)</td>
<td>142,47 € + 95,48 € = 237,95 €</td>
</tr>
<tr>
<td>Endoscopic treatment with rubber bands (3 gastroscopies + 3 rubber bad kits)</td>
<td>1,573,17 €</td>
</tr>
<tr>
<td>Hemodynamic study</td>
<td>221,78 €</td>
</tr>
<tr>
<td>Propranolol (cost/year of treatment)</td>
<td>69,64 €</td>
</tr>
</tbody>
</table>

Costs were calculated according to “Servicio de Información Económica, Hospital General Universitario de Alicante”, for 2004. Drug cost was calculated according to market prices for 2004.

**Analysis of effectiveness**

Effectiveness was expressed as the relative frequencies of patients free of rebleeding at the end of the monitoring period. The incremental effectiveness ratio (ICER) was calculated as the difference in relative frequency of rebleeding between patients undergoing a hemodynamic study and patients classified according to the size of varices. Each cost-effectiveness ratio was calculated by dividing the cost of each strategy by the non-bleeding patient rate at the end of the monitoring period. The result obtained was the cost per non-bleeding patient per year. ICER was calculated as: ICER = (cost A - cost B)/(effectiveness A - effectiveness B), where A is the most efficient strategy to obtain a positive denominator.
Lower and upper confidence interval boundaries for the relative frequencies were calculated using a binomial distribution (14).

RESULTS

In group 1, 36% of patients were "good responders" to propranolol, and the rebleeding rate was 0% after one-year monitoring; 17% of "non-responders" presented with recurrent variceal bleeding. In group 2 we observed that the bleeding frequency from grade I-II varices was 28%. These patients underwent prophylaxis with propranolol and the recurrence rate in one year was 28%. Bleeding rate due to large varices (grade III-IV) was 80%. These patients underwent endoscopic band ligation (EBL) and were treated with propranolol. Rebleeding in this group was 13%.

Cost results

Performing a hemodynamic study increases therapy cost by 221.78 € in each patient (from 11,408.55 to 11,630.33 €) before starting the prophylactic strategy. This increase represents hardly 19.6% of the cost caused by the bleeding event for 5 days. Considering the total cost at the end of the year, the lowest-cost therapeutic option is the one in which patients with small esophageal varices do not undergo hemodynamic study and are treated with propranolol (11,478.19 €). The cost for good responders undergoing a hemodynamic study and treated with propranolol was 11,699.97 €. Both patients presenting with large varices and non-responders represented a higher cost at the expense of endoscopic treatment (13,337.80 and 13,489.94 € each). These costs are higher for these patients suffering from another bleeding event (Table III).

Table III shows that treatment for good responders and non-responders is more expensive than treatment for patients classified according to variceal size. Despite this, when the cost is considered on the basis of the expected recurrence and non-recurrence rate, the cost increases by 576.67 euros (when the hemodynamic study is not performed). Values range from saving 3478.51 euros when a hemodynamic study is performed to an increase of 3580.11 euros. This fluctuation depends on the frequency of recurrence in each group.

95% CIs shown in brackets (lower boundary; upper boundary). Upper GI bleeding = Upper gastrointestinal bleeding. All costs in euros.
Results of effectiveness

Expected probabilities (expressed as relative frequencies) for each branch are shown in figure 1. Data from patients who underwent a hemodynamic study are taken from a prospective study performed in our Service. According to this study, 36% of patients were good-responders (N = 9), and none of them presented with rebleeding during the following year (relative frequency 0.00: 95% CI: 0.00-0.34). The rebleeding rate among non-responders (64% of patients; N=17) was 0.17 (95% CI: 0.03-0.38). Rebleeding frequency in patients with small varices treated with propranolol and nitrates was 0.25 (95% CI: 0.17-0.35), whereas in patients with large varices treated with drugs and RBL was 0.13 (95% CI: 0.08-0.21).

Annual bleeding recurrence frequency per year was 0.11 (95% CI: 0.02-0.27) in the group of patients classified according to the hemodynamic study, and 0.16 in the group treated according to the size of varices. The effectiveness of the hemodynamic study or the rate of patients free of rebleeding in a year was 0.89 (95% CI: 0.64-0.98), and the effectiveness of the classification according to variceal size was 0.84 (95% CI: 0.75-0.90).

Cost-effectiveness ratio

The cost-effectiveness ratio for the hemodynamic study was 15,843.25 (95% CI: 9,777.46-23,960.01) euros per patient free of rebleeding after one-year monitoring. The cost-effectiveness ratio for the strategy based on variceal size was 17,267.25 (95% CI: 14,329.94-20,875.65) euros per patient free of rebleeding after one-year monitoring.

ICER is 14,416.76 euros per patient not rebleeding after one-year monitoring as a consequence of the hemodynamic study.

Sensitivity analysis

The percentage of good responders in the hemodynamic study was different, keeping 20% patients with small varices. The percentage of patients with large/small varices was modified, keeping 36% of good responders in the hemodynamic study. Figure 2 shows that the percentage fluctuation of patients with small varices causes a slight alteration in the incremental cost when compared to hemodynamic study performance. On the other hand, the percentage of good responders in the hemodynamic study has a significant influence on the economic result. Thus, when the percentage is lower than 20% a hemodynamic study is not considered as cost-effective as the classification of patients according to variceal size. The strategy based on the hemodynamic study is cost-effective when the percentage of good responders is higher than 20%. Likewise, we performed an analysis in which rates for good responders and non-responders in the hemodynamic study, and rates for small and large varices established in the initial model were assumed as fixed. Recurrence rates were altered in both groups in the study (Fig. 3). In this case, the rebleeding rate for good responders and non-responders is considered the most important factor regarding cost-effectiveness. Rebleeding rate in the
group of patients with small varices must be 0% or lower than 5% for patients with large varices so that the strategy of a hemodynamic study is not cost-effective. On the other hand, a hemodynamic study is not cost-effective when rebleeding in the good-responder group is higher than 15%, and higher than 25% in the group of non-responders. Both percentages are higher than the maximum value of the 95% CI calculated from our experience.

DISCUSSION

Monitoring the hepatic venous pressure gradient (HVPG) prior to the prophylaxis of variceal bleeding is a useful procedure according to the results obtained in this study. Gradient measuring combined with medical or/and endoscopic treatment may reduce costs by 576.67 euros. The cost-effectiveness of HVPG monitoring to pilot the prophylaxis of variceal bleeding depends on the costs of gradient measuring, life expectancy, and rebleeding rate (15).

In Hicken et al. (16) HVPG measuring is an expensive strategy to reduce variceal bleeding and mortality, especially in patients with a low life expectancy. In Imperiale et al (17) the cost-effectiveness of HVPG measuring changes according to the sensitivity analysis. According to our results, a strategy based on a hemodynamic study is cost-effective when the good-responder rate is higher than 20%. On the other hand, a hemodynamic study in not cost-effective when the rebleeding rate in the good responder group is higher than 15%, or higher than 25% in the non-responder group. Both values are higher than the maximum value of the 95% CI calculated from our experience.

Treatment subsequent to the hemodynamic study reduces rebleeding recurrences in a year in the group classified according to the study: 0.11 (95% CI: 0.02-0.24) against 0.15 (95% CI: 0.08-0.25) in the group of patients treated according to the size of varices. This might be because gradient measuring monitors the response to treatment and optimizes it according to the latter.

None of our good responders (N = 9) treated with propranolol rebled during the following year (relative frequency 0.00). This may be explained by several factors: first, a lower complication rate ensues because most patients presented with hepatopathy as Child-Pugh class A-B (8.1 ± 2). Second, a short monitoring period may explain the absence of rebleeding. We find this study interesting because in our country (Spain) there are no data available to establish cost-effectiveness for the introduction of this procedure in clinical practice. Costs considered are the ones calculated by our hospital ("Hospital General Universitario de Alicante"). These might not be the same as costs in a free market, but they are representative of our National Health Service.

Hemodynamic markers optimize the prophylactic treatment of esophagogastric variceal bleeding and avoid the use of beta-blockers in patients having no benefit from them and their possible side effects.

In conclusion, we find that performing a hemodynamic study is a cost-effective tool in the prophylaxis of variceal bleeding for cirrhotic patients. A hemodynamic study reports a favorable cost-effectiveness ratio for as long as the recurrence rate of bleeding is lower than 20% for patients undergoing the study, and higher than 5% in patients not doing so. In addition, hemodynamic markers optimize the prophylactic treatment and avoid using therapeutic measures in patients obtaining no benefit from them.

REFERENCES


