Primary prophylaxis of variceal bleeding in liver cirrhosis: failure to learn from past experience

SAUMIL K SHAH, HIRALAL G DESAI
Department of Gastroenterology, B Y L Nair Hospital, Mumbai 400 008 and *Jaslok Hospital and Research Center, Mumbai 400 026

In patients with cirrhosis of liver, variceal bleeding is the most serious complication, with a mortality of up to 50%. Primary prophylaxis of variceal bleeding with shunt surgery or endoscopic variceal sclerotherapy was attempted and then abandoned, as higher rates of complications and mortality were observed. Endoscopic variceal ligation is now being recommended for primary prophylaxis in some centers, as it has fewer complications than sclerotherapy. But this has been done with inadequate evaluation of the cost-effectiveness of variceal ligation. Propranolol therapy is also being widely used for a selected group of patients (large varices with cherry red spots), despite its several limitations and side effects, to reduce frequency of bleeding but without improving survival. Is primary prophylaxis of variceal bleeding cost-effective? The cost involved needs to be accurately assessed in different countries. [Indian J Gastroenterol 2001; 20:64-67]

Key words: Esophageal varices, pharmacotherapy, portal hypertension, variceal band ligation

The most common and serious complication of portal hypertension in patients with cirrhosis of liver is variceal bleeding. Varices are present in 60% of decompensated and in 30% of compensated patients with cirrhosis of liver. About 30% of deaths in cirrhotics are due to variceal bleeding. In cirrhotic patients, the incidence of bleeding from esophageal varices is 10% per year in grade I-II and 20%-30% per year in grade III-IV varices. Increase in varix size from small to large occurs in 10%-20% of patients by 1 year after their first detection.

Only 35% of patients with cirrhosis and varices experience an episode of variceal bleeding during their lifetime. Endoscopic (size of varices, red color sign) and clinical (Child C status) criteria predict a higher risk of bleeding.

The aim of primary prophylaxis of variceal bleeding is to prevent the first variceal bleed, to avoid the mortality of up to 50% (within 6 weeks) associated with such bleeding. Shunt surgery in the 1960s and endoscopic variceal sclerotherapy (EVS) in the 1980s were performed for primary prophylaxis, but were soon abandoned as complications and mortality were higher in the treated group. At present, pharmacotherapy in all centers or endoscopic variceal ligation (EVL) in a few centers is recommended for primary prophylaxis. We need to discuss whether primary prophylaxis is cost-effective to justify its continuation.

Endoscopic variceal sclerotherapy or ligation
EVS has the advantage of simplicity, wide availability and easy acceptability by patients.

The largest randomized controlled trial showed an almost two-fold increase in mortality in patients with alcoholic cirrhosis receiving prophylactic EVS. EVS in cirrhotic patients reduces the incidence of the first variceal bleed and even prolongs survival, if only high-risk patients are selected and endoscopic ‘experts’ perform the procedure. EVS cannot be recommended for routine prophylaxis because of high (25%) complication rate, and the risk of procedure-related bleeding is greater than that of spontaneous bleeding. A combination of EVS and propranolol has also shown no advantage.

EVL has a distinct advantage over EVS by being “bloodless,” independent of expertise, and requiring shorter procedure time and fewer sessions, with minimal local and no systemic complications. The disadvantages are a high recurrence rate of varices (necessitating repeat therapy) and cost. Primary prophylaxis with EVL recommended in patients with large varices, was reported to be superior to propranolol therapy. However, this study had an unusually high rate of bleeding (43%) in the propranolol group, a mean dose of propranolol used (70 mg/day), lack of information on bleeding from nonvariceal sources, and no significant change in overall or bleeding mortality.

An earlier study comparing EVL with no therapy had reported 39% bleeding in the latter group at a mean follow up of 14 months. In cirrhotic patients, EVL was comparable to propranolol therapy. Lay et al showed a 2-year cumulative bleeding rate of 19% and death rate of 28% in the EVL-treated group as compared to 60% and 58% in controls, respectively. EVL is recommended to patients with large varices, in whom propranolol therapy is contraindicated or not tolerated.

Pharmacotherapy
Nonselective beta-blockers (propranolol and nadolol)
cause a greater portal pressure reduction compared to selective beta-blockers. Meta-analysis of 9 trials that included 996 patients using beta-blockers versus placebo had shown a reduction in the incidence of first bleed with the drug (odds ratio 0.54 [0.39-0.74]); only 2 of the 9 trials were, however, double blind. Poynard analyzed 4 trials that included 586 patients with large varices and showed actuarial rate of bleeding of 22% in the beta-blocker group as compared to 35% in the control group over a 2-year follow-up (p=0.002).19

Beta-blocker therapy, however, has several limitations: 1. Since only 35% of patients with varices bleed during their lifetime,4 a majority of patients receive unnecessary therapy. 2. With beta-blockers, the bleeding incidence is reduced by only 20% as compared to placebo.20 3. Side effects (dyspnea, asthenia, bradycardia, hypotension, cardiac insufficiency and impotence) are observed in 14%-27% of patients, necessitating stoppage of medication in half of them.19,21 Nadolol is not metabolized by the liver and has fewer side effects, necessitating its stoppage in only 4% of patients.22 4. Beta-blockers are contraindicated in patients with chronic obstructive lung disease, cardiac failure, heart block, peripheral vascular disease and diabetes mellitus. Several contraindications and frequent side effects make propranolol suitable for only 23% of patients. 5. Hepatic encephalopathy may be precipitated in patients with severe liver disease.23 6. The risk of bleeding and mortality is maximum in Child C cirrhosis and these are the patients in greatest need of primary prophylaxis; however, these patients respond poorly to propranolol.19 7. Propranolol does not reduce the hepatic venous pressure gradient (HVPG) in all cirrhotic patients with varices; a decrease in HVPG of more than 20% was seen in 34%, and a smaller or no decrease in 33% each. In spite of maximal tolerated doses of propranolol, 20% of patients did not respond at all.24 8. Monitoring of therapy in patients on pharmacotherapy is difficult as there is no correlation between the decrease in HVPG and heart rate or propranolol plasma levels.24 9. Abrupt discontinuation of propranolol leads to rebound increase in portal venous pressure with a higher risk of bleeding.25 and hence prophylactic therapy has to be lifelong.10 Even in patients who tolerated the drug without side effects, compliance was poor in almost one-third, during a 1-year follow up.26 11. With primary prophylaxis, the frequency of bleeding is reduced but the overall mortality or mortality due to bleeding is not significantly reduced.27

Isosorbide-5-mononitrate (IM) is used in patients in whom beta-blockers are contraindicated or cause side effects. IM has the advantages of complete bioavailability, more sustained pharmacological action, absence of hepatic metabolism and of first-pass effect, and normal pharmacokinetics even in patients with liver cirrhosis. Although the efficacy of IM has been found to be comparable to that of beta-blockers,28 prolonged use of IM may increase the advanced vasodilatory state and mortality in cirrhotic patients more than 50 years old.19 Nadolol plus IM is significantly more effective (bleeding risk 12%) than either drug alone (29%), with fewer side effects.19 The addition of IM to propranolol may convert nonresponders to propranolol to responders. Gross et al29 suggest that although the incidence of first variceal bleeding is reduced with medical therapy, the effect on longevity is minimal, and hence primary prophylaxis should be reserved for the few in whom a high risk of variceal bleeding is expected.

Shunt or transplant
Shunt surgery guarantees freedom from variceal bleeding in the presence of a patent shunt but has significant mortality in the emergency (50%) or elective (5%-10%) set-up and increases the incidence of encephalopathy (40%); further, it hastens deterioration of liver function. Survival is longer in medically treated patients.

Transjugular intrahepatic portosystemic shunt is preferred to operative shunt surgery for the management of variceal bleeding in Child B and C patients. It is not recommended for primary prophylaxis because of complications like shunt blockage (50% at 6 months) and encephalopathy (25%), and its high cost.30

Liver transplantation is a therapeutic alternative for patients with advanced cirrhosis of liver. However, primary prophylaxis for variceal bleed is not an indication for liver transplantation because of significant operative mortality and morbidity, the need for life-long immunosuppressive therapy, high cost and donor shortage even for seriously ill patients.

Is any prophylactic therapy cost-effective then?
In cirrhotic patients the issue of cost-effectiveness of primary prophylaxis with propranolol, sclerotherapy and shunt surgery was studied.23,24 Propranolol was found to be the only cost-effective form of prophylaxis, but life expectancy was increased by only 0.1-0.4 years. The cost of endoscopic examinations was not included.

Primary prophylaxis requires at least one endoscopy (in all cirrhotics) to look for the presence or absence of varices. Repeat endoscopy every three years was recently recommended in those with no varices and every one year in those with grade I varices, to check for progression. If primary prophylaxis is not routinely recommended, endoscopy is not essential in patients with cirrhosis of liver. This would lead to significant cost saving (Table).

The critical question is not whether a procedure or drug is marginally effective and is safe in reducing variceal bleeding, but whether it significantly prolongs
Table: Cost of primary prophylaxis of variceal bleed in cirrhosis of liver

<table>
<thead>
<tr>
<th>Procedure</th>
<th>Rupees</th>
</tr>
</thead>
<tbody>
<tr>
<td>Initial upper GI endoscopy</td>
<td>500*</td>
</tr>
<tr>
<td>Repeat endoscopy every year for those with grade I varices (x 3)</td>
<td>1500</td>
</tr>
<tr>
<td>Repeat endoscopy every 3 years for those with no varices (x 2)</td>
<td>1000</td>
</tr>
<tr>
<td>Assuming average cost of upper GI endoscopy</td>
<td></td>
</tr>
<tr>
<td>Rs 1500 per patient for 100 patients</td>
<td>150,000</td>
</tr>
<tr>
<td>Assuming varices present in 35 of 100 patients (large varices in approximately 20)</td>
<td></td>
</tr>
<tr>
<td>Cost of propranolol in 20 patients</td>
<td></td>
</tr>
<tr>
<td>(Rs 1000/y for 2 y per patient)</td>
<td>40,000</td>
</tr>
<tr>
<td>Cost of band ligation in 20 patients</td>
<td></td>
</tr>
<tr>
<td>(Rs 20,000 for 3 sessions per patient**)</td>
<td>400,000</td>
</tr>
<tr>
<td>Cost with propranolol for 100 patients</td>
<td></td>
</tr>
<tr>
<td>150,000 + 40,000 = 190,000 per treated patient</td>
<td>9500</td>
</tr>
<tr>
<td>Cost with band ligation for 100 patients</td>
<td></td>
</tr>
<tr>
<td>150,000 + 400,000 = 550,000 per treated patient</td>
<td>27,500</td>
</tr>
</tbody>
</table>

*Cost in private hospital average Rs 1500 excluding travel
**Cost of 8 + 5 + 5 bands

survival and is cost-effective. Despite observing higher mortality in the treated group with shunt surgery and EVS for primary prophylaxis, we are now experimenting with EVL and pharmacotherapy without appreciating the high cost involved for reduction of risk of bleeding without significantly improving survival.

References


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Correspondence to: Dr Desai, 16 Krishna Kunj, 30 Chowpatty Road, Mumbai 400 007. Fax: (22) 384 5400. E-mail: desaimg@hotmail.com

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NEWS AND NOTICES

A Hepatology Update will be held in New Delhi March 16 and 17, 2001.
For details contact: Prof P Kar, Organizing Secretary, Room No. 111, 1st Floor, B L Taneja Block, Department of Medicine, Maulana Azad Medical College, New Delhi 110 002
Tel: (11) 323 6437, 688 9271, 323 3400 Ext 4452 Fax: (11) 687 2515. E-mail: pkar@del6.vsnl.net.in

The National Conference on Telemedicine will be held in Lucknow April 23 - 27, 2001.
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