Motion – Prophylactic banding of esophageal varices is useful: Arguments against the motion

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Bleeding from esophageal varices leads to substantial morbidity and mortality. Despite advances in pharmacological and endoscopic therapy, as well as general supportive care, the mortality rate associated with acute variceal hemorrhage has not improved significantly over the past two decades. Prophylactic therapy with nonselective beta-blockers or long acting nitrates reduces the incidence of variceal bleeding in patients with cirrhosis, is cost effective and may improve survival. Surgical portosystemic shunting reduces the risk of bleeding but is associated with significant operative mortality and a high risk of portosystemic encephalopathy. Endoscopic sclerotherapy causes adverse effects in a large proportion of patients and is, therefore, not suitable for primary prophylaxis of bleeding. Although variceal band ligation is effective in reducing the rate of bleeding and is safer than sclerotherapy, it has not been shown to provide a survival advantage compared with beta-blockers. A significant reduction in the rate of variceal bleeding with band ligation, compared with beta-blockers, was shown in only one study. Beta-blockers offer several advantages, including low cost, ease of use and safety. The available data do not yet support the prophylactic use of variceal band ligation, and this procedure should be reserved for patients who are either unwilling or unable to take beta-blockers. It is hoped that additional large, multicentre trials of band ligation versus beta-blockers will examine the efficacy, cost effectiveness and impact on quality of life among patients with cirrhosis.

Key Words: Band ligation; Beta-blockers; Cirrhosis; Endoscopic sclerotherapy; Esophageal varices

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Esophageal varices are a major cause of admission to hospital in North America for gastrointestinal bleeding. The direct costs associated with variceal bleeding among patients with cirrhosis were estimated at more than US$4 billion as far back as 20 years ago. Furthermore, despite advances in supportive care and specific pharmacological and endoscopic therapy, the mortality from an episode of variceal hemorrhage has not changed significantly since that time. One explanation for this disappointing fact is that many patients experience catastrophic hemorrhage and are thus unable to reach an intensive care setting for treatment. Of patients who are admitted to hospital for their first episode of variceal hemorrhage, 30% to 50% die within six weeks.

VARICEAL HEMORRHAGE

It is reasonable to assume that the early identification of patients with esophageal varices and treatment to prevent the first episode of bleeding may improve the prognosis. Several studies have found that the prevalence of varices in patients with cirrhosis is approximately 60% (1). Of these patients, 25% to 40% experience their first variceal hemorrhage within the first two years of the diagnosis, and most occur within the first year. The major predictors of variceal bleeding include the severity of the underlying liver disease and the size and visual characteristics of the varices. For example, large size and the presence of red wale markings, identified at endoscopy, portend a high risk of variceal bleeding.

The underlying physiological cause of esophageal variceal bleeding is portal hypertension. This state is characterized by increased blood flow in the splanchic circulation and increased intrahepatic vascular resistance. The degree of portal hypertension is reflected by the hepatic venous pressure gradient (HVPG), which is the difference in pressure between the portal and hepatic veins. It therefore provides a measurement of the portosystemic pressure gradient. A gradient of greater than 12 mmHg is associated with an increased risk of bleeding from esophageal varices, whereas reduction of the HVPG to below this threshold essentially eliminates the risk of variceal bleeding.

PROPHYLACTIC THERAPY

Primary prophylaxis involves the application of treatment that is designed to prevent the first episode of variceal bleeding in patients with cirrhosis. Several treatment modalities have been tried, including portosystemic shunts, medications (especially beta-adrenergic antagonist and long acting nitrates), endoscopic sclerotherapy, and rubber band ligation. Early studies showed that surgical shunts reduced the risk of bleeding but were associated with unacceptable operative mortality and a high risk of portosystemic encephalopathy. A number of trials, involving more than 1500 patients, have investigated the role of endoscopic sclerotherapy in primary prophylaxis. With some exceptions, the trials found that sclerotherapy was not a worthwhile treatment, even though the risk of bleeding was reduced, largely because of high rates of adverse effects, such as pulmonary complications, fever, chest pain and esophageal ulceration.

The administration of propranolol, a nonselective beta-blocker, results in a 9% to 23% decrease in HVPG. Although this results mainly from a decrease in portal venous inflow due to mesenteric arteriolar vasoconstriction, high doses of this agent may further reduce the HVPG by decreasing the heart rate and cardiac output. Approximately 1000 patients have been enrolled in nine randomized placebo-controlled trials of beta-blockers, usually propranolol or nadolol, for primary prophylaxis of variceal bleeding (2-4). Unfortunately, the patient populations were not similar in the studies. A 25% reduction in the resting heart rate was used as a measure of beta-blockade. Treatment with beta-blockers was shown to reduce the relative risk of variceal bleeding by 45% and to reduce mortality by 20% after two years of therapy. The risk of death from hemorrhage was reduced by approximately 50%. The rates of first variceal hemorrhage with beta-blockers ranged from a low of 3% to 5% to a high of 20% to 35%, whereas the rates in control subjects were 18% to 35%. The overall one-year survival rates were 75% to 95% in the beta-blocker groups compared with 66% to 89% in the control groups. Multivariate analysis revealed that failure to respond to these drugs was associated with young age, large varices, advanced liver disease and low medication dosage. Beta-blockers are tolerated well by most patients, and fewer than 5% were withdrawn from the clinical trials because of adverse effects.

Long acting nitrates have also been shown to be effective at reducing the risk of bleeding, but are generally considered to be second-line drugs for patients who do not tolerate beta-blockers. One study found that the combination of beta-blockers and nitrates was associated with a lower rate of bleeding than treatment with beta-blockers alone, but other investigators have not confirmed this.

RUBBER BAND LIGATION

Band ligation has mainly replaced endoscopic sclerotherapy for the acute treatment of bleeding esophageal varices. The former is more effective than sclerotherapy for acute bleeding, causes fewer complications and requires fewer sessions to eradicate the lesions. It has, therefore, been proposed that band ligation be used in the primary prophylaxis of esophageal varices. Published studies have compared this technique with treatment with either placebo or beta-blockers. Given the proven safety and efficacy of beta-blockers in primary prophylaxis, it is generally considered unethical to conduct a placebo-controlled trial.

A prospective, randomized trial involving 126 patients with cirrhosis and endoscopically evaluated high-risk varices found that band ligation decreased the risk of first bleeding compared with untreated controls (19% versus 60%, P=0.0001) (5). The two-year cumulative mortality rate was lower in the ligation group than in the control group (28% versus 58%, P=0.0011). Most deaths in the ligation group were due to complications of bleeding, without a large impact of liver disease. In contrast, the mortality rate was high in the control group, most deaths due to liver failure.
Prophylactic banding of esophageal varices

CONCLUSIONS

Beta-blockers are of proven benefit for the prevention of first variceal hemorrhage. Surgery and sclerotherapy are less suitable, because of adverse effects. Band ligation therapy is clearly superior to no active treatment for primary prophylaxis. The current data do not, however, demonstrate a reduced risk of bleeding compared with beta-blockers, except in one study. Furthermore, band ligation does not enhance survival compared with beta-blockers. Given that beta-blockers are inexpensive, widely available, convenient and generally very safe, they should be used for primary prophylaxis against variceal hemorrhage. Band ligation should be reserved for patients who are unwilling or unable to take beta-blockers.

REFERENCES

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