

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

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Variceal hemorrhage is a frequent complication of cirrhosis and is associated with a high mortality rate, especially in patients with decompensated liver disease. Endoscopy is useful in identifying factors that predict a high likelihood of bleeding, including large varices and red colour signs. Endoscopic rubber band ligation has superseded sclerotherapy in the prevention of both recurrent hemorrhage and the first episode of bleeding, because it causes fewer complications and requires fewer sessions to eradicate varices. It has been proven to be more effective than nontreatment in the primary prophylaxis against variceal hemorrhage. There is extensive literature that has found that band ligation is more effective than beta-adrenergic receptor antagonists at preventing the first variceal hemorrhage. There is ongoing debate about the relative merits of these two approaches, but the available evidence supports the conclusion that band ligation is the treatment of choice in the primary prevention of variceal bleeding. Trials of combined medical and endoscopic therapy are eagerly awaited, and the author suspects that it may prove to be more effective than either modality alone.

Key Words: *Band ligation; Beta-adrenergic receptor antagonists; Prophylaxis; Variceal hemorrhage*

Proposition – La ligature prophylactique des varices œsophagiennes est utile : arguments favorables

RÉSUMÉ : Les hémorragies variqueuses sont une complication fréquente de la cirrhose et elles sont associées à un taux élevé de mortalité, surtout chez les patients atteints d'une hépatopathie décompensée. L'endoscopie aide à déceler les facteurs de risque élevé d'hémorragie comme les grosses varices et les signes de rougeur. La ligature élastique des varices par endoscopie a remplacé la sclérothérapie pour la prévention des hémorragies récurrentes et de l'apparition du premier épisode de saignement parce qu'elle entraîne moins de complications et qu'elle nécessite moins de séances pour détruire les varices. La technique s'est révélée plus efficace que la non-intervention dans la prophylaxie primaire des hémorragies variqueuses. Selon de nombreux documents, la ligature élastique est plus efficace que les antagonistes des récepteurs bêta-adrénergiques pour prévenir un premier épisode d'hémorragie variqueuse. Les mérites relatifs de chacune des deux formes de traitement font toujours l'objet de débat, mais les données existantes étayent la conclusion selon laquelle la ligature élastique est le traitement de première intention pour la prévention primaire des hémorragies variqueuses. On attend avec impatience les résultats d'essais associant le traitement médical et le traitement endoscopique, et l'auteur est d'avis que la bithérapie pourrait s'avérer plus efficace que la monothérapie, sous une forme ou une autre.

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Therapy for preventing the first variceal hemorrhage should be undertaken in the context of the natural history of patients with esophageal varices. Approximately 30% of patients with compensated cirrhosis (Child-Pugh class A and early class B) and 60% of patients with decompensated disease (class C and advanced class B) have esophageal varices (1). Overall, 25% to 30% of patients with known esophageal varices bleed from them within a two-year period (2). The first variceal hemorrhage is associated with mortality rates as high as 30% to 50% and the risk of death is inversely related to liver function, as indicated by the Child-Pugh class (1). Patients with large varices, particularly those with red colour signs, and decompensated cirrhosis are at the greatest risk of bleeding and are most likely to die from it. If untreated, high-risk patients may have as much as a 40% chance of bleeding within one year and a 60% chance within two years (3).

PROPHYLACTIC THERAPY

There are two viable means of preventing variceal hemorrhage. Drug therapy with propranolol or other nonspecific beta-adrenergic antagonists reduces the hepatic venous pressure gradient (HVPG), which is measured by catheterizing a hepatic vein and determining the difference between free and wedged hepatic vein pressures. Although these medications decrease the risk of variceal hemorrhage, they have not consistently been shown to reduce mortality (4).

Other drugs, such as isosorbide-5-mononitrate, may be of value either alone or in combination with beta-adrenergic antagonists. The combination of nitrates with beta-blockers reduces portal pressure more than does either drug given alone. Nevertheless, the long term effects of nitrate therapy are uncertain and they can provoke liver failure, particularly in older patients (5). A major drawback to drug therapy is the fact that patients must be compliant with a lifelong regimen. Complications of medication are usually not life-threatening, but approximately 20% of patients are not able to tolerate (or have a contraindication to) propranolol. Moreover, more than half of treated patients may not achieve the desired 20% reduction in HVPG (6).

Endoscopic treatment to prevent the first variceal hemorrhage is not employed widely outside of Japan. Endoscopic sclerotherapy was examined in several western studies, with mixed results (7). Most endoscopists in western countries abandoned the prophylactic use of sclerotherapy because the technique has not proved to be consistently superior to receiving no active treatment at all. One large trial from the United States was halted early because patients in the prophylactic sclerotherapy arm experienced more complications and a higher mortality than those in the control group (8).

BAND LIGATION

Rubber band ligation is recognized as the method of choice for endoscopically preventing recurrent variceal hemorrhage in patients who have already experienced bleeding.

This is known as secondary prophylaxis. Many prospective randomized comparisons of endoscopic band ligation with sclerotherapy for secondary prevention of bleeding have confirmed that the newer technique is associated with fewer complications, a lower incidence of recurrent hemorrhage, more rapid eradication of varices and improved survival (9).

Band ligation versus no active treatment

Prevention of the first variceal hemorrhage (primary prophylaxis) was studied in six prospective randomized trials that compared endoscopic ligation with no treatment (3,10-14). These six trials included 675 patients. Three of the trials revealed a statistically significant reduction in the incidence of first variceal bleeding in patients treated with endoscopic ligation. Two studies found that active treatment resulted in a significant reduction in bleeding-related mortality, and one found a significant reduction in mortality from all causes.

Results from five of these trials were analyzed recently using meta-analysis (15) that found that band ligation reduced the absolute risk of first variceal hemorrhage from 18% to 4%. The relative risk reduction was 64%, and four patients would need to be treated to prevent one episode of first variceal bleeding. The relative risk reduction for mortality from all causes was 45%. Five patients would need to be treated with band ligation to prevent one death. The incidence of treatment-related complications in these five trials was very low. The single major reported problem was an esophageal perforation related to the use of the endoscopic overtube in one patient. This problem has since been eliminated by the introduction of multiple-fire ligating devices that do not require the use of an endoscopic overtube. The design of these studies has since been widely criticized because beta-adrenergic blockers, which have been proved effective, were not employed in the comparator group.

Band ligation versus beta-blockers

Six prospective randomized trials compared endoscopic ligation with beta-adrenergic receptor blockade for the primary prevention of variceal hemorrhage. Two were published as complete papers (16,17) and four as abstracts (18-21). These six trials included 360 patients. Two of the trials showed a statistically significant reduction in the incidence of first variceal bleeding in patients treated with endoscopic ligation. None of the studies found a significant difference in mortality rates, and there were no serious complications in either treatment group.

Meta-analysis of four of the six trials revealed that the absolute risks for first variceal bleeding were 15.7% and 7.6% with beta-blockers and band ligation, respectively (15). The relative risk reduction for patients in the endoscopic treatment groups was 52%. Thirteen patients would need to be treated with endoscopic ligation rather than beta-blockade to prevent one episode of first variceal bleeding. The meta-analysis uncovered no reduction in bleeding-

related mortality or in mortality from all causes. A second meta-analysis (published in abstract form) analyzed all six trials (22). It found that the relative risk reduction for first variceal hemorrhage in patients given endoscopic therapy was 44%. Fifteen patients would need to be treated with endoscopic ligation rather than propranolol to prevent one episode of variceal bleeding. There was no difference in mortality rates between the two groups.

Trial by Sarin and colleagues

Sarin et al (17) conducted the largest trial (involving 89 patients) comparing beta-blockade with endoscopic ligation that has been published in full manuscript form. This study deserves detailed discussion. After 18 months of treatment, the actuarial probability of bleeding was 43% in the propranolol group and 15% in the ligation group. In an accompanying editorial, Burroughs and Patch (23) attributed the high incidence of bleeding in the propranolol group to the fact that a low dose of medication was employed. The average daily dose of propranolol in this trial was 70 mg, whereas the average in previous studies was 123 mg (range 40 to 300 mg) (4). This is a plausible explanation, but not the only one. The reader is not told, for example, the average height or weight of the patients in this study. If Sarin's patients were smaller or lighter than those in trials from other countries, the 70 mg dose might have been perfectly appropriate.

Most early trials that compared beta-adrenergic blockade with no treatment for the primary prevention of variceal hemorrhage did not focus on high-risk patients with large varices, but included more heterogeneous study populations. Only some patients were at high risk for bleeding. For example, only four of the nine widely cited trials specifically enrolled patients with medium or large varices (24). More relevant, perhaps, is the observation that only one of these nine beta-blocker trials had more Child-Pugh class C patients than did the Sarin study, two did not discuss the Child-Pugh classification, and four of the remaining six either included fewer than 10% Child-Pugh class C patients or none at all (4). The Sarin study (17) contained approximately 50% Child B and 30% Child C patients in each treatment arm, and 14 of the 16 patients who experienced bleeding had advanced liver disease. It is widely acknowledged that treatment with beta-adrenergic antagonists is especially beneficial for patients with medium or large varices, but the efficacy of drug therapy in patients with both advanced liver disease and large varices may be smaller.

Contraindications and poor compliance are the two major shortcomings of pharmacological treatment. Sarin et al (17) excluded eight of 52 otherwise eligible patients from their study because of contraindications for the use of propranolol. Two additional patients were withdrawn during the study because of adverse effects of the medication. The authors checked compliance with the drug regimen by measuring heart rates and interviewing the patients at monthly intervals for three months and then at intervals of

every third month. This methodology is similar to that employed by other investigators. Given the long interval between compliance assessments and the fact that bleeding in the majority of propranolol-treated patients occurred after more than four months of follow-up, it is reasonable to speculate that some of the patients did not take the medication consistently or might have even discontinued it altogether. Abrupt cessation of beta-blocker treatment is known to be associated with an increased risk of hemorrhage (25). In contrast to the relatively late timing of bleeding in the propranolol-treated patients, only one of five patients who bled after undergoing ligation therapy did so after the first two months of follow-up. This finding confirms the widely held opinion that, once the varices have been ligated, the risk of bleeding is reduced dramatically.

CONCLUSIONS

What can we conclude from the trials that have examined endoscopic ligation as primary prophylaxis for variceal bleeding? Endoscopic ligation is an effective and safe alternative to the use of beta-adrenergic receptor antagonists. Indeed, all available data indicate that endoscopic treatment is associated with a lower incidence of first variceal hemorrhage than drug therapy. There appears to be no difference in overall survival between the two treatment methods. However, this might be a reflection of the small number of patients studied thus far. Several additional large studies comparing endoscopic with pharmacological treatments, and including actual cost and quality of life assessments, are needed before it can be determined which modality is superior. Looking forward, I believe that the combination of pharmacological and endoscopic therapies may be superior to either treatment given alone. Studies that are aimed at answering this question should be undertaken.

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