Primary Prophylaxis for Variceal Bleeding: Are We There Yet?

Liver disease and especially cirrhosis remain a significant public health burden in the world. Cirrhosis is the 10th leading cause of death in the United States accounting for 1.1% of all deaths. Gastroesophageal varices are present in approximately 50% of patients with cirrhosis and bleeding from varices is one of the complications of portal hypertension that leads to significant morbidity and mortality. Recent studies have shown that survival has improved over the past 2 decades in patients who have bled from varices. The in-hospital mortality rate has declined steadily from 42.6% in 1980 to 14.5% in 2000. Despite these improvements, mortality from bleeding varices remains high and thus prevention of the initial bleed, primary prophylaxis, remains an area of interest and controversy.

Most experts agree that β-blockers are the preferred therapy for prevention of the first bleed from esophageal varices. This belief is based on effectiveness (a 50% reduction in risk of bleeding), cost (less than endoscopic or surgical therapy), and ease of administration. Unfortunately, many patients either have a contraindication to the use of β-blockers or they are intolerant of the drugs thus limiting their usefulness. Endoscopic therapy has been proposed as an excellent way to prevent bleeding in patients with varices. Although sclerotherapy was effective in some studies, the high incidence of side effects, cost, and lack of uniformity of the results in the different studies limited enthusiasm for this approach. The advent of variceal band ligation (VBL) and demonstration that it is superior to sclerotherapy has again raised the issue of whether endoscopic therapy is better than pharmacologic therapy in the prevention of the initial bleed from varices.

A meta-analysis of studies published before 2001 suggested that VBL was superior to β-blocker therapy. Since 2001 four more studies comparing VBL to β-blockers have been published as complete reports, including the most recent in this issue of GASTROENTEROLOGY by Jutabha et al bringing the total number of published complete reports to 6. The studies are relatively uniform as to size of varices (medium to large) and use of β-blockers. Obvious differences in these studies are the number of patients enrolled (30–152), length of follow-up (11 to 34 months), percentage of patients with Child’s C cirrhosis (13% to 33%), numbers of patients with alcoholic cirrhosis (10%–70%), and length of time between banding sessions (1 to 6 weeks). Two of the 6 studies showed a significantly reduced risk of bleeding in those receiving VBL and in one mortality was less in those receiving VBL as compared to β-blockers. In the other studies no significant differences in the primary end points of variceal bleeding or death were observed.

In the study of Sarin et al cumulative rate of variceal bleeding was 9% in those who received VBL whereas 27% bled in the β-blocker group. The concern about this latter study is the high bleeding rate in the β-blocker treated patients compared with previous reports. In the report of Jutabha et al the rate of variceal bleeding with β-blockers was 13% (about the expected rate) but the rate of bleeding with VBL was 0%, much below the rates observed in previous studies.

There are a number of reasons as to why the current study may have shown such low bleeding rates with VBL. The study was terminated early by the investigators because of significant differences in both rates of bleeding and mortality between the VBL and β-blocker treated patients. In well-designed clinical trials the investigators are blinded to the results of the study and a Data Safety Monitoring Board follows the results of the trial thus preventing either premature stopping or prolonging a study that has shown no or a significant difference between the groups of subjects. Termination of this study seems premature when one closely examines the data. First, the investigators power analysis estimated that 104 patients would be required to achieve a statistically significant difference between the 2 groups with expected rates of bleeding in the VBL group of 4% and 19% in those receiving β-blockers. This is an overly optimistic estimate of the risk of variceal bleeding following VBL as in the previously published studies the lowest risk observed with VBL was 7% with an average risk of at least 10%. If a 10% failure rate for VBL had been used for the power calculation, then many more patients would have been required to correctly power the study and this expected rate of bleeding would have suggested to the investigators that the absence of bleeding in the VBL group was by chance and not due to the therapy.

With early termination and a short period of follow-up, the number of patients enrolled was small as
were the number of end points, 4 episodes of variceal bleeding and 4 deaths, leading this author to be concerned about the value of the statistical difference found by the investigators. By χ² analysis with Yates’ correction I found the difference in the failure rate between the 2 groups barely significant (P = .03) and that the rates of variceal bleeding and death were probably not significantly different (P = .12). If there was one episode of variceal bleeding or death in the band ligation group, then statistical significance would not be achieved irrespective of the test used (P = .35). Thus, in the only 2 studies in which statistically significant differences were found in favor of VBL, there is concern that bleeding rates with β-blockers were unusually high in one and bleeding rates with VBL were too low in the second. In those studies in which the observed bleeding rates were closer to the expected rates no statistically significant differences were observed. In the study with the largest number of patients and longest follow-up the risk of bleeding with either therapy was virtually the same.

If β-blockers and VBL are equivalent therapies, and I believe that they are, then is it possible to improve on the effectiveness of either? Recently Sarin et al performed a randomized, controlled trial comparing VBL with and without a β-blocker in the primary prevention of variceal bleeding. The actuarial probability of bleeding at 20 months in the VBL plus β-blocker vs VBL alone groups was 7% vs 11% respectively (difference not significant). The addition of sclerotherapy to VBL also does not appear to improve efficacy. It may be possible to improve the efficacy of β-blocker therapy by monitoring the response of the hepatic venous pressure gradient (HVPG). The risk of bleeding in patients whose HVPG falls to below 12 mm Hg or by at least 20% with β-blocker therapy is significantly less than those who fail to achieve this response. Thus, it is possible that monitoring β-blocker therapy by measuring the patients’ HVPG before and after treatment and using VBL in those who fail to respond may be an effective way to prevent variceal bleeding. However, controlled trials are needed before we embrace this approach.

It has been more than 20 years since Lebrec et al made the seminal observations that nonselective β-blockers lower portal pressure and reduce the risk of variceal bleeding. After numerous controlled trials, nonselective β-blockers remain the treatment of choice for the primary prevention of variceal bleeding. VBL should be considered in patients who are intolerant of β-blockers or in whom β-blocker therapy is contraindicated. We need further studies on the role of HVPG measurement in the management of these patients and new drugs need to be developed that are at least as effective as β-blockers in the prevention of variceal bleeding but with less side effects. Lastly, it is essential that these studies have sufficient power to answer the questions posed.

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References

Commensal Flora: Wolf in Sheep’s Clothing

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The adult intestinal tract generally is in a state of peaceful co-existence with the complex milieu of microbes. The mucosal epithelial barrier provided by a pre-epithelial layer and a well-developed mucosal immune network has evolved to respond to a range of microbial environmental states including colonization, commensalism, symbiosis, persistent infections, and pathogen-induced disease. The commensal/symbiotic gut ecosystem protects host mucosal surfaces from pathogenic bacteria, enhances nutrient uptake, and primes the mucosal immune system. This mixed species “genome” is central to normal immune development and epithelial function.

A successful defense depends upon a variety of mechanisms, including physical barriers provided by epithelial cells, and recognition of invading organisms by epithelial cells and resident dendritic cells that result in signaling and production of additional antimicrobial products, as well as inflammatory cytokines. There is a growing recognition of the key role of innate immune mechanisms in intestinal mucosal homeostasis. Innate immunity uses preformed and rapidly synthesized effectors and sensors and rapid activation of cellular transcription and protein synthesis, to mount a prompt response to pathogen/commensal challenge, eliminating the microbe, and returning the tissue to a basal, functional state with minimal pathology.

In the gastrointestinal tract, the innate immune system has evolved to recognize a wide range of endogenous and exogenous ligands, by so-called pattern recognition receptors (PRRs). Although initial attention focused on the ability of ligands from pathogen bacteria to bind the innate immune receptors it is clear that commensal bacteria are also capable of triggering PRRs. In addition, at least some recent studies have suggested that Toll-like receptors (TLRs) sense commensal organisms during inflammation and other insults, and in mice protect epithelial cells from injury. However, these previous studies have not examined the innate and acquired immune responses in the context of physiological and pathological inflammation induced by nonpathogenic microbes. The innate immune response in the intestinal tract also appears capable of contributing to natural tolerance to commensal organisms. Moreover, recognition of these ligands can occur on the cell surface, inside the cell, and at distant sites from the epithelial barrier. The ability of microbes to translocate within the intestinal mucosal tissues to mesenteric lymph nodes further expands the host cells available for the microbe to interact with.

The innate immune network is comprised of several components. Distinct classes of PRR are central to innate immunity. To date, more than 10 TLRs that recognize pathogen products either singly or in combination have been identified. Caterpillar or NOD family members function as intracellular sensor molecules for immune detection and modulate signals from pathogens. The expression of these proteins in the intestinal immune system is incompletely defined but preliminary data suggest that the subcellular compartment, cell, and site-specific expression determines effector responses. TLR5 is distributed predominantly on the basolateral surface of polarized intestinal epithelial cells.