

THE NON-OPERATIVE MANAGEMENT OF BLEEDING ESOPHAGEAL VARICES: ENDOSCOPIC, PHARMACOLOGICAL OR BOTH?

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Life threatening hemorrhage secondary to ruptured esophageal varices is a common complication of portal hypertension. The mortality rate associated with the index bleed is 35%; on the recurrent bleed, it is 50%.^{1,2,3} Between 10-20% per year will experience their first bleeding after varices are diagnosed and rebleeding may be experienced within two years in 70% of patients.^{4,5} While it is most important to control actively bleeding varices, it is also necessary to prevent effectively the index bleed (primary prevention), as well as, recurrent variceal bleeding (secondary prevention).

The aggressive resuscitation of the bleeding patient in order to achieve hemodynamic stability is the most important and urgent therapy. This is then followed by an endoscopic attempt to locate and control the bleeding vessel. In the meantime. Maneuvers to preserve the remaining liver function and eliminating other risk factors which may push the liver to fail are simultaneously instituted.

The identification of the bleeding varix is often difficult in an episode of massive bleeding. During the resuscitative process

several pharmacological agents can be administered in order to reduce or stop the hemorrhage so that diagnostic, as well as, definitive therapeutic procedures can be instituted expeditiously. Prompt endoscopy has a very high diagnostic yield. However, most of the times the severity of the bleed and the blood clots in the esophageal lumen hampers significantly the localization and identification of the bleeding vessel. Such situations effectively reduce the success rates of endoscopic interventions. Successful outcomes are often assured if a good visibility of the operative field is achieved by a vigorous gastric and esophageal lavage, balloon tamponade or pharmacological agents which diminishes or halts, albeit temporarily, the active bleed.

In the latter part of this century, the endoscopic methods of stopping variceal hemorrhage are the treatment of choice. It can eradicate almost all varices following several treatment sessions. Newer techniques, i.e., band ligation have improved outcomes and reduced remarkably attendant serious complications.

Prevention of the Index Variceal Hemorrhage

Pharmacological Agents:

A meta-analysis⁶ involving 797 patients in seven primary prevention trials of large esophageal varices showed that patients treated with nonselective beta adrenergic blockers had 47% overall reduction in bleeding episodes, 45% reduction in deaths due to bleeding and 22% reduction in total mortality. These advantages were more apparent in Child's A and B patients compared to Child's C patients. In patients presenting with ascites, Poynard, et al⁷ have found that beta-adrenergic blockers are effective in preventing the first variceal bleeding both in patients with and without ascites.

Endoscopic Therapy

Over 19 RCT's have compared sclerotherapy with comparable groups for preventing the first variceal bleed. While the early trials have positive results, the latter ones failed to confirm early encouraging results with prophylactic sclerotherapy. Most notably, the studies were either poorly designed or weakly conducted. The heterogeneity of the survival data makes it difficult to give meaningful assessment of potential survival benefits of endotherapy.

Lately, Sarin, et al⁸ has shown that prophylactic variceal band ligation is safe and more effective than propranolol in the primary prevention of variceal bleeding.

Control of Active Variceal Bleeding

Pharmacological Agents

Pharmacological therapy is either administered to a bleeding patient upon admission, e.g. vasopressin, somato-

statin, etc. or as prophylaxis against the first bleed or to subsequent bleeds after successful endoscopic variceal eradication, e.g. propranolol, nadolol, subcutaneous octreotide.

Vasopressin or vasopressin with nitroglycerin has been proven effective in the acute control of variceal hemorrhage. The latter preparation is associated with less vasoconstrictive complications and a meta-analysis of three studies showed that vasopressin and nitroglycerin is superior to vasopressin alone. By lowering splanchnic pressures, intravenous infusion of somatostatin or its analogues, i.e. octreotide have demonstrated efficacious control of variceal hemorrhage comparable to injection sclerotherapy. Somatostatin has been shown to be more effective in the control of active bleeding when compared to vasopressin, depression, endoscopic sclerotherapy or balloon tamponade. Octreotide, a long-acting analogue of somatostatin, has comparable outcomes with vasopressin, terlypressin, or endoscopic sclerotherapy.⁹⁻¹²

Endoscopic Therapy

Endoscopic hemostatic techniques have effectively replaced surgery as the gold standard in the management of bleeding varices. The endoscopic control of variceal hemorrhage may be achieved by endoscopic injection sclerotherapy (EIS) or band ligation (EBL). In both procedures the ultimate goal is complete eradication of the varices. Sclerotherapy however is associated with a number of well-described complications. Variceal obliteration is usually achieved by several weekly repeat procedures after the initial endoscopic control. In EBL, complications like sepsis, large ulcers (which may bleed in the interim), esophageal strictures, perforation, etc. are significantly less. However, scabs of the necrotic esophageal mucosa may be prominent enough to hamper

the endoscopic view in the subsequent treatment sessions. A recent meta-analysis¹⁰ showed that EBL is associated with lower mortality rates and better survival rates. In EBL, the interval between treatment sessions tends to be farther apart, i.e. 10-14 days. Meta-analysis¹³ of several studies comparing sclerotherapy and variceal ligation has shown that patients treated with variceal ligation have faster variceal eradication, lesser rebleeding rates, transfusion requirements, complications and mortality rates. In addition, endoscopic variceal ligation is easy to perform and teach to trainees. At present, EBL is the preferred endoscopic therapy due to the many advantages described above.

Combination of pharmacological agents and endotherapy

Recently, the efficacy of a combination of pre-endoscopy infusion drip with somatostatin or its analogues followed by endoscopic diagnosis and endotherapy after resuscitation has been looked at. It seems that immediate IV infusion of these compounds may control variceal bleeding efficiently resulting into a cleaner esophageal lumen and thus, a smoother administration of endoscopic therapy.

Combined or sequential management of active variceal bleeding can be the trend for the future. Pre-endoscopy administration of vasoactive drugs can effectively lower splanchnic pressures and results in cessation of active variceal hemorrhage. The cleaner esophageal lumen gives the endoscopist distinct advantage of a clearer working area when instituting definitive endoscopic homeostatic methods after the patient has been resuscitated satisfactorily. An RCT¹⁴ has demonstrated that somatostatin and endoscopic sclerotherapy is significantly better to somatostatin alone in the control of active variceal bleeding. It seems that immediate IV infusion of these compounds

may control variceal bleeding efficiently resulting into a cleaner esophageal lumen and thus, a smoother administration of endoscopic therapy. Nowadays, most bleeding patients are admitted to the hospital, are resuscitated with blood and fluid replacement, placed on somatostatin IV drip and scheduled for a more "elective" therapeutic endoscopy session later in the day or the next morning when the endoscopy team and other support facilities are functioning smoothly. The European ABOVE study¹⁵ has determined that pre-endoscopy infusion of somatostatin facilitates performance of sclerotherapy and ultimately improves significantly its efficacy. It should be noted that the study was terminated early because the interim analysis revealed a substantial difference in treatment failures in the placebo group.

Prevention of recurrent variceal bleeding

Pharmacological agents

Propranolol reduces the portal pressure by lowering splanchnic pressures and decreasing cardiac rate. Earlier, Lebrec and co-workers⁷ have demonstrated that lowering the basal heart rate by 25% with propranolol can significantly prevent the index variceal hemorrhage (primary prevention) and/or rebleeding (secondary prevention). A meta-analysis⁶ of several RCT's looking at prevention of secondary variceal bleeding, involving mostly propranolol, showed that prolonged beta-blocker treatment significantly reduced the occurrence of variceal bleeding, and deaths from variceal bleeding, and overall mortality. However, symptomatic cardiac side effects of prolonged beta-blockade, seen in approximately 3 to 27% have resulted in patients withdrawing from this treatment regimen. Compared to sclerotherapy, a meta-analysis¹⁶ of nine RCT's showed that endoscopic sclerotherapy is more effective than propranolol in the

prevention of variceal bleeding although no difference in the patient survival between the two treatment groups was observed. Because of the high incidence of adverse events associated with sclerotherapy, propranolol has been judiciously recommended as the first choice treatment for preventing variceal rebleeding.

Endoscopic therapy

Of the eight published RCT's comparing sclerotherapy and propranolol in the prevention of recurrent variceal bleeding, three favored propranolol and four did not show any difference. Several studies comparing band ligation with injection sclerotherapy have demonstrated the early variceal rebleeding is lower in those treated with band ligation. The latter is also associated with less local complications in the esophagus, e.g. strictures, perforations, etc. in the long-term prevention of rebleeding; the regular endoscopic monitoring and subsequent "prophylactic" endotherapy of reformed varices should be the schedule of choice.

Combination of Pharmacological Agents and Endotherapy

The New Italian Endoscopic Club has demonstrated in a placebo-controlled randomized trial¹⁷ that adding somatostatin to patients undergoing endoscopic sclerotherapy to prevent recurrent variceal bleeding does not decrease the incidence of early rebleeding. Another RCT¹⁸ also noted that octreotide plus sclerotherapy is superior to sclerotherapy alone in the prevention of early rebleeding while another study did not demonstrate advantages of the combination therapy. When propranolol was added to sclerotherapy, Avgerinos¹⁶ showed that there is a two-fold improvement in efficacy, from a bleeding risk of 59% to a risk of 25%. Two RCT's demonstrated that combined propranolol and sclerotherapy may be more

superior to sclerotherapy alone in the reduction of recurrent variceal bleeds. It has been reported recently that patients maintained with propranolol after complete endoscopic variceal obliteration by band ligation have significantly longer intervals of rebleeding. One RCT¹⁹ showed that combined nadolol and isosorbide-5 mononitrate is better than sclerotherapy, especially when the HVPG is less than 12 mm Hg. We²⁰ found combination of octreotide and sclerotherapy to be superior to sclerotherapy alone in the management of acute variceal bleeding.

CONCLUSIONS

In the view of above, we can conclude that endoscopic therapy maintains a pivotal role in the management of variceal bleeding. The optimal treatment for acute variceal bleeding is a regimen consisting of combined endoscopic treatment combined with vasoactive drugs. In addition, drugs like propranolol in combination with endoscopic therapy should be used for the secondary prophylaxis of variceal bleeding.

REFERENCES

1. Silverstein FE, Gilbert DA, Tedesco FJ, et al. The national ASGE survey on upper gastrointestinal bleeding: study design and baseline data. *Gastrointest Endos* 1981; 27: 73.
2. Hassan F, Levine BA. The role of endoscopic sclerotherapy in the management of esophageal varices. *Dig Dis*. 1992; 1 (Suppl: 10): 38.
3. Cello JP, Chan MF. Octreotide therapy for variceal hemorrhage. *Digestion*. 1993; 1 (Suppl: 54): 20.
4. Navarro VJ, Garocia T. Variceal hemorrhage. *Gastrointest Emerg* 1995; 11: 391.
5. Papiaro L D, Amico G, Pasta L, et al. Portal hypertension in cirrhosis; Natural history.

- In: Bosch J, Ciroszmann RJ (eds). Portal hypertension. Pathophysiology and treatment. Oxford: Blackwell, 1994; 72.
6. Hayes P, Davis J, Lewis J, Bouchier I. Meta-analysis of value of propranolol in prevention of variceal hemorrhage. *The Lancet* 1990; 336: 153
 7. Bernard B, Lebrec D, Mathurin P, Opolon P, Poynard P. Propranolol and sclerotherapy in the prevention of gastrointestinal rebleeding in patients with cirrhosis: a meta-analysis. *Journal of Hepatology* 1997; 26: 312.
 8. Sarin SK, Lamba GS, Kumar M et al. Comparison of endoscopic ligation and propranolol for the primary prevention of variceal bleeding. *NEJM* 1999; 340: 988.
 9. Pedretti G, Elia G, Calzetti C, Magnani G, Fiaccadori F. Octreotide versus terlypresine in acute variceal hemorrhage in liver cirrhosis (Emergency control and prevention of early rebleeding). *Clinical investigator* 1994; 72: 653.
 10. Imperiale T, Teran JC, Mc, Culough A. A Meta-analysis of somatostatin versus vasopressin in the Management of acute esophageal variceal hemorrhage. *Gastroenterology* 1995; 109;
 11. McKee R, Sandostatin Therapy of Acute Esophageal variceal bleeding. *Digestion* 1993; 54 (Suppl 1): 27.
 12. Sung J, Chung S, Chi-Wai Lai, Chan E, Leung J, Man-Yee Yung, Kassianides C, Li A. Octreotide infusion for emergency sclerotherapy for variceal Hemorrhage. *Lancet* 1993; 342: 637.
 13. Besson J, Ingrand P, Person B, Boutroux D, Heresbach D, Bernard P, Hochain P, Larrico J, Gourlaouen A, Ribard D, Mostefa Kara N, Legoux JL, Pillegard B, Becker MC, Di Costanzo J, Metreau JM, Siavin C, Beauchant M. Sclerotherapy with or without octreotide for acute variceal bleeding. *The new England Journal of Medicine* 1995; 33: 55
 14. Villanueva C, Ortiz J, Sabat M, Gallego A, Torras X, Soriano G, Sainz S, Boadas J, Cusso X, Guarner C, Balanzo J. Somatostatin alone or combined with emergency sclerotherapy in the treatment of acute esophageal bleeding: A prospective randomized trial. *Hepatology* 1999; 30: 84.
 15. Avgerinos A, Nevens F, Raptis S, Fevery J, ABOVE Study Group. Early administration of somatostatin and efficacy of sclerotherapy in acute esophageal variceal bleeds: the European Acute Bleeding Esophageal Variceal Episodes (ABOVE) randomized trial, *Lancet* 1997; 350: 494.
 16. Avgerinos A, Rekoumis G, Klonis C, et al. Propranolol in the prevention of recurrent upper gastrointestinal bleeding in patients undergoing endoscopic sclerotherapy. A randomized controlled trial. *J Hepatol* 1993; 19: 01-311.
 17. Primignani M, Andreoni B, Carpinelli L, et al. New Italian Endoscopic club. Sclerotherapy plus octreotide versus sclerotherapy alone in the prevention of early rebleeding from esophageal varices: A randomized, double-blind placebo controlled multi center trial. *Hepatology* 1995; 21: 322.
 18. Beretta L, Motta R, De Franchis R, New Italian Endoscopic club. Sclerotherapy plus Octreotide versus sclerotherapy alone in the prevention of early rebleeding from esophageal varices: A randomized, double-blind placebo controlled multi-center trial. *Hepatology* 1995; 21: 322.
 19. Grace N. Diagnosis and Treatment of gastrointestinal bleeding secondary to portal hypertension. *American Journal of Gastroenterology* 1997; 92: 1081.
 20. Farooqi JJ, Farooqi RJ, Haq NU, et al. Treatment and outcome of variceal bleeding. A comparison of two methods. *JCPSP Vol. 10 (4): 131.*