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-analysis involving 797 patients in seven primary prevention trials of large esophageal varies 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 al have found that beta-adrenergic blockers are effective in preventing the first variceal bleeding both in patients with and with out 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 al 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, somatostatin, 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 splanchic 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, terlipressin, or endoscopic sclerotherapy.

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-analysis 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-analysis 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. 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 study 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 coworkers 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-analysis 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-analysis 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 recom-
mended as the first choice treatment for
preventing variceal rebleeding.

Endoscopic therapy

Of the eight published RCT's compar-
ing sclerotherapy and propranolol in the
prevention of recurrent variceal bleeding,
three favored propranolol and four did not
show any difference. Several studies com-
paring 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 ran-
domized trial that adding somatostatin to
patients undergoing endoscopic sclerotherapy
to prevent recurrent variceal bleeding does
not decrease the incidence of early rebleeding.
Another RCT 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
c sclerotherapy, Avgerinos 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 main-
tained with propranolol after complete
endoscopic variceal obliteration by band
ligation have significantly longer intervals of
rebleeding. One RCT showed that
combined nadolol and isosorbidde-5 mono-
nitrate in better than sclerotherapy, espe-
cially when the HVPG is less than 12 mm
Hg. We 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 com-
bined 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.

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