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Abstract

Variceal bleeding is a life-threatening complication of portal hypertension with a six-week mortality rate of approximately 20%. Patients with medium- or large-sized varices can be treated for primary prophylaxis of variceal bleeding using two strategies: non-selective beta-blockers (NSBBs) or endoscopic variceal ligation (EVL). Both treatments are equally effective. Patients with acute variceal bleeding are critically ill patients. The available data suggest that vasoactive drugs, combined with endoscopic therapy and antibiotics, are the best treatment strategy with EVL being the endoscopic procedure of choice. In cases of uncontrolled bleeding, transjugular intrahepatic portosystemic shunt (TIPS) with polytetrafluoroethylene (PTFE)-covered stents are recommended. Approximately 60% of the patients experience rebleeding, with a mortality rate of 30%. Secondary prophylaxis should start on day six following the initial bleeding episode. The combination of NSBBs and EVL is the recommended management, whereas TIPS with PTFE-covered stents are the preferred option in patients who fail endoscopic and pharmacologic treatment. Apart from injection sclerotherapy and EVL, other endoscopic procedures, including tissue adhesives, endoloops, endoscopic clipping and argon plasma

coagulation, have been used in the management of esophageal varices. However, their efficacy and safety, compared to standard endoscopic treatment, remain to be further elucidated. There are safety issues accompanying endoscopic techniques with aspiration pneumonia occurring at a rate of approximately 2.5%. In conclusion, future research is needed to improve treatment strategies, including novel endoscopic techniques with better efficacy, lower cost, and fewer adverse events.

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Key words: Esophageal varices; Primary prophylaxis; Variceal bleeding; Secondary prophylaxis; Cirrhosis; Endoscopic treatment

Core tip: Endoscopic therapy is the major treatment option in the management of patients with esophageal varices and liver cirrhosis. The current treatment guidelines recommend the use of endoscopic therapy in both primary and secondary prophylaxis, as well as in the setting of the acute bleeding episode, along with pharmaceutical agents. This review summarizes data from randomized clinical trials and prospective clinical studies along with meta-analytical data, when applicable, to present the most updated recommendations for the endoscopic management of esophageal varices.

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INTRODUCTION

In patients with liver cirrhosis, esophageal varices are portosystemic collateral venous channels related to por-

tal hypertension. The gold standard for the diagnosis of esophageal varices is esophagogastroduodenoscopy (EGD) which must be performed at the time of cirrhosis diagnosis^[1]. In addition, other methods, such as platelet count, spleen size, portal vein diameter, transient elastography, and capsule endoscopy, have also been assessed in esophageal varices diagnosis^[2,3]. In compensated cirrhosis (absence of varices at baseline endoscopy), EGD should be repeated every two to three years, whereas in patients with small varices, every one to two years. In the setting of decompensation, EGD for variceal screening should be performed annually^[1]. Hepatic venous pressure gradient (HVPG) is a surrogate marker of portal hypertension and values > 10 mmHg are predictive of variceal formation and decompensation^[4]. Variceal bleeding occurs when HVPG is ≥ 12 mmHg^[5,6]. HVPG values > 20 mmHg are associated with failure to control bleeding, early rebleeding, and mortality in the setting of acute variceal bleeding^[7]. Although HVPG measurement is a significant prognostic indicator of cirrhosis, it is performed only in few centers, as it is an expensive and invasive procedure. Variceal bleeding is a life-threatening complication of portal hypertension. However, mortality rates have declined due to the progress in the management of patients with esophageal varices and acute variceal bleeding (AVB)^[8]. Furthermore, advances in endoscopic techniques have also significantly contributed to the improved survival rates.

Randomized clinical trials (RCTs) and prospective studies were evaluated for (1) the prophylaxis of first variceal bleeding; (2) the management of the acute bleeding episode; and (3) the secondary prophylaxis of rebleeding from esophageal varices. Collected data were used to assess the role of endoscopic treatment using meta-analytical data analysis, when applicable, in an effort to report the most recent advances in the treatment of esophageal varices. The role of endoscopic treatment *vs* no intervention or other treatments, in patients with liver cirrhosis and esophageal varices, was assessed.

ENDOSCOPIC TREATMENT AS A PRIMARY PROPHYLAXIS OF VARICEAL BLEEDING

The term primary prophylaxis refers to the prevention of the first variceal bleeding in patients with liver cirrhosis. According to the Baveno V consensus, there are two main strategies for the primary prophylaxis of AVB from medium or large varices^[9]. These include either the administration of non-selective beta-blockers (NSBBs) or repeated sessions of endoscopic variceal ligation (EVL) until variceal eradication.

NSBBs act by decreasing HVPG values to < 12 mmHg or by $\geq 20\%$ from baseline one to three months after the initiation of treatment. The acute hemodynamic response to beta-blockers (20 min after the administration of propranolol) has been shown useful in predicting

the long-term risk of first bleeding by reducing HVPG by $\geq 10\%$ from baseline values^[10,11]. Bureau *et al*^[12] studied HVPG in 34 cirrhotic patients before and after treatment with NSBBs (20 patients were treated for primary prevention and 14 for secondary prevention). The non-responders, characterized as those not showing a decrease of HVPG values to < 12 mmHg or by $\geq 20\%$ from baseline, received isosorbide-5 mononitrate. Among the 20 patients (59%) with a hemodynamic response, variceal bleeding occurred in 10%, as compared to 64% in 14 non-responders. Endoscopic therapies have a local effect on reducing wall tension by obliterating the varices. However, these therapies lack the ability to decrease portal venous inflow or resistance.

Sclerotherapy

Endoscopic injection sclerotherapy has been evaluated as a primary prophylaxis^[13]. This method is invasive, expensive, and associated with potential life-threatening complications. Therefore, sclerotherapy has been abandoned as a viable option in the treatment of esophageal varices^[14-16].

EVL vs no intervention

Meta-analysis of eight RCTs^[17] comparing EVL to no treatment showed EVL reducing both the risk of first portal hypertensive bleeding (OR = 0.3, 95%CI: 0.17-0.53) and mortality (OR = 0.42, 95%CI: 0.3-0.6) (Table 1) with no statistical heterogeneity for either bleeding or mortality.

EVL vs NSBBs

A recent meta-analysis included 19 RCTs with 1504 patients, of which 731 had the EVL arm, and 773 had the beta-blockers arm. In this study, propranolol was used in 17 trials, while nadolol and carvedilol were each used in one trial^[18]. In total, 176/731 patients (24.1%) randomized to EVL and 177/773 patients (22.9%) randomized to NSBBs died. Random effects model meta-analysis showed no difference in mortality between the intervention groups (Table 1). EVL appeared to have a beneficial effect on upper gastrointestinal bleeding (RR = 0.68, 95%CI: 0.52-0.90) and it reduced the incidence of variceal bleeding compared to NSBBs (13.0% *vs* 19.0% of patients) (Table 1). However, the beneficial effect of EVL on bleeding was not confirmed in subgroup analyses of trials with adequate randomization or in the full paper articles. No difference was observed between the two interventions regarding bleeding-related mortality (5.1% *vs* 6.3%, RR = 0.85, 95%CI: 0.53-1.39), whereas both interventions were associated with adverse events. Carvedilol ($n = 77$) in primary prophylaxis showed a significantly lower rate of first variceal bleeding compared to EVL ($n = 75$) (10% *vs* 23%, 95%CI: 0.19-0.96)^[19]. Overall mortality and bleeding-related mortality did not differ significantly between the two treatments (35% *vs* 37%, and 3% *vs* 1%, respectively). In the EVL group, six patients had banding ulcer-related bleeding.

Table 1 Endoscopic treatment as a primary prophylaxis of variceal bleeding in patients with cirrhosis

Treatment comparisons	No. of trials	Number of patients	Bleeding OR (95%CI)	Mortality OR (95%CI)
EVL vs NT	8	738	0.3 (0.17-0.53)	0.42 (0.3-0.6)
NSBBs vs EVL	19	1504	0.66 (0.45-0.96)	1.09 (0.92-1.30)

EVL: Endoscopic variceal ligation; NSBBs: Non-selective beta-blockers; NT: No treatment.

EVL with NSBBs vs NSBBs

Combination treatment of EVL and beta-blockers is not recommended for primary prophylaxis of variceal bleeding. Gheorghe *et al*^[20] randomized 72 patients with high-risk esophageal varices listed for liver transplantation to receive either combined treatment of EVL with propranolol or propranolol monotherapy. Six percent of patients in the combination group and 31% in the monotherapy group had a bleeding episode during follow-up (mean: 18 mo). The actuarial probability of bleeding-free survival, after follow-up, was 96% (the combination) and 69% (monotherapy). Another randomized study used cirrhotic patients with high-risk for esophageal varices treated with either EVL plus nadolol ($n = 70$) or nadolol monotherapy ($n = 70$)^[21]. Their results showed no statistical difference in a 26-mo follow-up period between the two groups for upper gastrointestinal bleeding (26% vs 18%, respectively). Variceal bleeding did occur in 14% ($n = 10$) and 13% ($n = 9$) of the patients, respectively. Mortality was the same in both groups ($n = 16$ in each arm). Adverse events were more frequent in the combination treatment compared to the monotherapy group (68% vs 40%). The two episodes of variceal bleeding were attributed to ligation.

Only one RCT, including 144 patients (12% non-cirrhotic portal hypertension), compared EVL with propranolol ($n = 72$) to EVL monotherapy ($n = 72$)^[22]. The actuarial probability of the first bleed at 20 mo was 7% in the propranolol group and 11% in the EVL monotherapy group. Similarly, the actuarial probabilities of overall and bleeding-related mortalities were comparable between the two groups.

Summary

The current treatment guidelines suggest two treatment strategies, NSBB or EVL, in the prevention of first variceal bleeding of medium and large esophageal varices^[9]. Considering that both treatment options have the same efficacy, the selection criteria should include other important issues such as adverse effects and cost. There are safety issues concerning EVL in the primary prophylaxis of variceal bleeding. In a previous study, EVL and no treatment were compared with intolerance or contraindications to beta-blockers in cirrhotic patients^[17]. This trial was stopped prematurely due to increased bleeding in the EVL group, which was presumed mostly iatrogenic. In a prospective cohort study, patients with contraindications,

intolerance or no-response to beta-blockers and treated with EVL achieved protection from variceal bleeding comparable to that of good beta-blocker responders^[23]. However, Reiberger *et al*^[24] recently demonstrated that the efficacy of EVL is limited in patients lacking hemodynamic response to NSBBs (propranolol or carvedilol). This was further supported by de Souza *et al*^[25], who showed that patients with first AVB while on treatment with NSBBs, had an increased risk for further bleeding and death, despite the addition of EVL. Although data regarding the risk for paracentesis-induced circulatory dysfunction in cirrhotic patients with refractory ascites following beta-blocker usage exist, further studies are needed to confirm these findings^[26]. Current evidence shows NSBBs to be effective in primary prophylaxis of variceal bleeding. Hence, these drugs could be considered a first-line treatment due to their effectiveness, inexpensiveness, ease of administration, and lack of adverse events. EVL is also a good treatment option, especially for patients with contraindications or intolerance to beta-blockers, and possibly patients with refractory ascites^[27]. The efficacy of EVL in non-responders to beta-blockers needs further evaluation, as current evidence is contentious. Novel drugs, decreasing portal pressure and improving hepatic endothelial dysfunction, need to be further investigated. Simvastatin, alone or combined with NSBBs, decreases HVP and liver perfusion in patients with cirrhosis, nonetheless, its beneficial effects require further confirmation^[28].

ENDOSCOPIC TREATMENT OF AVB

Cirrhosis-associated AVB is an emergent clinical condition which, depending on the underlying etiology of liver disease, has an incidence range of 5% to 15%, and a six-week mortality rate of approximately 20%^[29-31]. The major predictors of first variceal bleeding are advanced liver disease, the size of varices, the endoscopic presence of red wale marks^[32] and an HVP value > 12 mmHg^[33]. Baveno V guidelines recommend the combination of endoscopic, pharmacologic, and antibiotic treatment in the management of AVB^[9]. Usage of antibiotics upon admission significantly improves survival, suggesting bacterial infections may trigger variceal rupture^[34]. Upper gastrointestinal bleeding, when cirrhosis is suspected, should be treated promptly after admission with vasoactive agents, such as vasopressin, somatostatin, and their analogues, with continuous treatment for three to five days. Endoscopy should be performed within 12 h of admission. Endoscopic criteria for the AVB diagnosis are: (1) endoscopic presence of active bleeding from a varix; (2) the finding of a varix with a white nipple or clots; or (3) the presence of varices without any other source of bleeding^[35]. In patients with massive bleeding and/or presence of overt hepatic encephalopathy, airway protection with endotracheal intubation and mechanical ventilation should be performed, considering the high risk for aspiration^[36].

Table 2 Endoscopic treatment of acute variceal bleeding in patients with cirrhosis

Treatment comparisons	Number of trials	Number of patients	Failure to control bleeding OR (95%CI)	Mortality OR (95%CI)
Vasoactive drugs <i>vs</i> sclerotherapy	17	1817	-0.02 (-0.06-0.02)	-0.02 (-0.06-0.02)
EVL <i>vs</i> sclerotherapy	12	1309	0.025 (-0.004-0.046)	0.013 (-0.023-0.049)
Sclerotherapy + drugs <i>vs</i> sclerotherapy	8	1026	-0.132 (-0.181-0.084)	0.034 (-0.004-0.071)
Endoscopy + drugs <i>vs</i> endoscopy	8	939	1.12 (1.02-1.23)	0.73 (0.45-1.18)
Sclerotherapy + drugs <i>vs</i> drugs	4	400	-0.163 (-0.239-0.087)	-0.055 (-0.127-0.018)

EVL: Endoscopic variceal ligation.

Endoscopic treatment vs vasoactive drugs

A recent Cochrane meta-analysis of 17 trials compared the efficacy of vasoactive drugs with that of injection sclerotherapy^[37]. No significant differences were observed between the sclerotherapy and each vasoactive regimen for any outcome tested: (1) failure to control bleeding; (2) five-day treatment failure; (3) rebleeding; (4) mortality; (5) number of blood transfusions; and (6) adverse events. When combining all the trials, irrespective of the vasoactive drug, the results were similar (Table 2). However, there was a significant difference regarding adverse events (risk difference = 0.08, 95%CI: 0.03-0.14) and serious adverse events (risk difference = 0.05, 95%CI: 0.02-0.08) being more frequent with sclerotherapy. Thus, although injection sclerotherapy is as efficacious as vasoactive drugs in AVB, it is accompanied by a higher incidence of complications.

EVL has been compared to somatostatin in one RCT with 62 and 63 patients with AVB, in each treatment group respectively^[38]. Treatment failure was significantly lower in the EVL group (4.8%) compared to the somatostatin group (31.7%) with fewer transfusion requirements and a tendency towards a shorter hospital stay. However, the adverse events and 42-d mortality were similar.

Endoscopic treatment combined with vasoactive drugs vs vasoactive drugs

A meta-analysis showed that the combination of injection sclerotherapy with vasoactive agents had significantly fewer treatment failures to control bleeding compared to vasoactive drugs alone^[39]. Although a 5.5% survival difference was found favoring the combination group, it was not statistically significant (Table 2). A RCT showed that treatment failure (defined as active bleeding 72 h after treatment, no completion of EVL procedure or death), hospital stay, and transfusion requirements were less frequent in the group receiving a combination of EVL and octreotide compared to the group receiving octreotide monotherapy^[40].

Endoscopic treatment combined with vasoactive drugs vs endoscopic treatment

A meta-analysis of eight RCTs showed the combination of sclerotherapy with vasoactive drugs is better in controlling bleeding than sclerotherapy alone. However, there was no difference in survival between the two treatments

(Table 2)^[39]. Avgerinos *et al*^[41] showed that early administration of somatostatin, prior to emergency sclerotherapy, was more effective than placebo. Furthermore, patients receiving somatostatin had fewer transfusion requirements, less active bleeding at endoscopy, less need for rescue therapy, and lower rates of mortality. A combined endoscopic treatment (sclerotherapy or EVL) with somatostatin, octreotide, or vaptotide showed better initial bleeding control than endoscopy alone, as well as five-day hemostasis (RR = 1.28, 95%CI: 1.18-1.39), with a number needed to treat of eight and five, respectively^[42]. The significant difference remained even when: (1) using drugs other than octreotide; (2) including a low proportion of alcoholic patients (< 40%); or (3) excluding high-risk cirrhotic patients (< 35% of Child-Pugh C patients). However, mortality was not significantly decreased by the combined treatment (Table 2), and severe adverse events were similar in both groups.

Sclerotherapy vs EVL

EVL is, by consensus, the recommended endoscopic procedure, although sclerotherapy could be used if ligation is technically difficult^[9]. EVL has been shown to be significantly better in bleeding control compared to sclerotherapy, but with a difference of only 2.5%^[39]. The percentage difference for mortality was 1.3% in favor of ligation, although not statistically significant (Table 2). Villanueva *et al*^[43] randomly assigned patients with AVB receiving either intravenous somatostatin to EVL (*n* = 90) or injection sclerotherapy (*n* = 89). Ligation showed less failure to control bleeding than sclerotherapy (4% *vs* 15%) and resulted in a significantly higher six-week survival rate (83% *vs* 67%). The rate of complications (28% *vs* 14%) and the rate of major side effects (RR = 3.1, 95%CI: 1.1-9.1) were higher with sclerotherapy compared to EVL. However, subgroup analysis of patients with active bleeding showed that the therapeutic failure was not significantly different (sclerotherapy, 24%; EVL, 18%; RR = 1.3, 95%CI: 0.4-4.8). In an RCT, a sustained rise of portal pressure was observed after injection sclerotherapy for AVB (*n* = 25) with HVPG remaining high during the 120 h study period. On the other hand, HVPG returned to the baseline values within 48 h after EVL (*n* = 25)^[44]. This sustained HVPG increase, following sclerotherapy, might explain the higher rebleeding rate observed with sclerotherapy than with EVL (40% *vs* 12%) during the 42-d follow-up.

Management of uncontrolled variceal bleeding

The term uncontrolled variceal bleeding is used to describe continuous or recurrent (within five days) bleeding in spite of the initiation of the adequate pharmacologic and endoscopic treatment. The occurrence ranges for uncontrolled variceal bleeding are between 10% and 20%^[11]. Transjugular intrahepatic portosystemic shunt (TIPS) with polytetrafluoroethylene (PTFE)-covered stents is the “salvage” therapy of choice in this setting^[9].

Monescillo *et al.*^[45] evaluated high-risk variceal bleeders (HVPG ≥ 20 mmHg), randomly allocated to either receive TIPS ($n = 26$) within the first 24 h after admission or not. The non-TIPS group had significantly more treatment failures. Early TIPS placement reduced treatment failure, as well as both in-hospital and one-year mortality. However, potential issues with the study include a lack of continued pharmacologic therapy and EVL in the non-TIPS group, as well as usage of bare stents in the early-TIPS group. Furthermore, the decision to use TIPS was based on the HVPG measurement. In a subsequent study, García-Pagán *et al.*^[46] randomly assigned patients with cirrhosis and AVB with high probability for treatment failure (Child-Pugh class C < 14 points or Child-Pugh class B and active bleeding at endoscopy) to receive either standard pharmacologic and endoscopic treatment with TIPS with PTFE-covered stents (early-TIPS group, $n = 32$) or continued pharmacotherapy and EVL (pharmacotherapy-EVL group, $n = 31$). The pharmacotherapy-EVL group had a 50% one-year actuarial probability of remaining free of rebleeding compared to a 97% probability in the early-TIPS group. The one-year actuarial survival was 61% in the pharmacotherapy-EVL group and 86% in the early-TIPS group. However, the one-year actuarial probability of hepatic encephalopathy was 28% in the early-TIPS group compared to 40% in the pharmacotherapy-EVL group (95%CI: 18-40), which was not significantly different. No differences were observed between the two groups in terms of serious adverse events. The results of this RCT were supported by a later retrospective analysis of data from the same center^[47]. A recent study of early TIPS placement is also promising, with rebleeding, 30-d, and six-month mortality rates of 9.7%, 12.9%, and 19.3%, respectively^[48].

Balloon tamponade, as a single therapy, may control initial variceal hemorrhage in $> 80\%$ of cases^[49]. However, hemostasis is transient and it is associated with a high rate of complications (aspiration pneumonia, migration, necrosis of the esophagus, airway obstruction) and a mortality rate of 20%^[3]. It is recommended that balloon tamponade should only be used as a temporary bridge until definite treatment is applied, not exceeding 24 h of treatment^[9]. A new alternative to balloon tamponade is an SX-Ella Danis stent, a removable, covered, self-expanding metal stent that controls bleeding by tamponading the varices. In a case-series ($n = 10$), the safety and efficacy of SX-Ella Danis stents in refractory variceal bleeding were evaluated^[50]. This procedure had a bleeding control failure rate of 30% and overall 42-d mortality rate of

50%. Six patients survived the acute bleeding episode and had stents removed endoscopically at a median of nine days after insertion. One patient had a minor ulceration of the esophagus caused by stent insertion. Another case series involving seven patients with variceal bleeding that were nonresponsive to standard treatment reported an initial control of bleeding of 89%, followed by high five-day treatment failure (56%) and six-week mortality (77%) rates^[51]. A United Kingdom-multicenter RCT is in the process of recruiting participants for a study comparing SX-Ella Danis stents against standard endoscopic techniques for treatment of esophageal variceal hemorrhage (NCT01851564). A Spanish-based RCT is also in the process of recruiting patients with variceal bleeding that is refractory to medical and endoscopic therapy for a study comparing Danis stent with balloon tamponade (NCT01242280).

Summary

The available data suggest that emergency endoscopic treatment with EVL at the time of the initial diagnostic endoscopy should be the gold standard for the management of the AVB episode. Sclerotherapy can be used when ligation is technically difficult. The combination of EVL with vasoactive drugs given as soon as possible after admission is currently the best option. Emergency TIPS with PTFE-covered stents is a common practice in controlling bleeding from esophageal varices; however, only certain centers can offer this emergency service. Future randomized trials exploring the role of self-expandable esophageal stents should be performed.

ENDOSCOPIC TREATMENT AS A SECONDARY PROPHYLAXIS OF VARICEAL BLEEDING

After a variceal bleeding episode, there is a high risk for rebleeding and death. Rebleeding rate is approximately 60% with a mortality rate of 30%, one to two years after the initial bleeding episode^[52]. According to Baveno V, secondary prophylaxis should start as soon as possible in all patients with previous variceal bleeding, and the combination of NSBBs and EVL is the preferred treatment option^[9].

Sclerotherapy

Although sclerotherapy reduces the rates of variceal rebleeding and improves survival compared to no intervention, it is associated with frequent and potentially serious adverse events^[13]. Studies comparing sclerotherapy to NSBBs or in combination with NSBBs showed no difference in rebleeding or mortality rates^[12,53,54].

A recent meta-analysis showed that rebleeding was significantly less common with EVL than with sclerotherapy, without critical heterogeneity among trials^[13]. The number needed to treat with EVL to prevent one rebleeding episode was ten. EVL was also associated

Table 3 Endoscopic treatment as a secondary prophylaxis of variceal bleeding in patients with cirrhosis

Treatment comparisons	Number of trials	Number of patients	Rebleeding OR (95%CI)	Mortality OR (95%CI)
EVL <i>vs</i> sclerotherapy	20	1634	0.53 (0.42-0.67)	0.77 (0.59-0.99)
EVL <i>vs</i> NSBBs and IsMn	4	476	0.79 (0.62-1.00)	0.81 (0.61-1.08)
EVL <i>vs</i> EVL + NSBBs	9	955	0.59 (0.41-0.85)	0.71 (0.45-1.11)
EVL <i>vs</i> EVL + sclerotherapy	8	520	1.05 (0.67-1.64)	0.99 (0.68-1.44)
TIPS <i>vs</i> endoscopy	12	883	0.32 (0.24-0.43)	1.17 (0.85-1.61)

EVL: Endoscopic variceal ligation; IsMn: Isosorbide mononitrate; NSBBs: Non-selective beta-blockers; TIPS: Transjugular intrahepatic portosystemic shunt.

with significantly lower mortality rates when compared to sclerotherapy (Table 3). Complications were also less common in patients treated with EVL (pooled OR = 0.29, 95%CI: 0.19-0.44). To date, EVL is the endoscopic procedure of choice in this setting.

EVL vs EVL and sclerotherapy

A number of trials have compared the combination of EVL and sclerotherapy to EVL alone in achieving rapid and complete eradication of esophageal varices, but with conflicting results^[55]. The meta-analysis of these eight trials showed that there was no significant difference in variceal rebleeding, mortality, or number of endoscopic sessions to variceal obliteration in patients with EVL *vs* patients receiving the combination treatment of EVL and sclerotherapy (RR = 0.23, 95%CI: 0.055-0.51) (Table 3). Moreover, the incidence of esophageal stricture formation was higher in the combination group.

EVL vs NSBBs and isosorbide mononitrate

A meta-analysis of four randomized controlled trials including 476 patients assessed the efficacy and safety of NSBBs and isosorbide mononitrate (IsMn) *vs* EVL on the prophylaxis of variceal rebleeding^[56]. There were no significant differences in the rate of rebleeding, bleeding-related mortality (RR = 0.76, 95%CI: 0.31-1.42), overall mortality, or complications (RR = 1.26, 95%CI: 0.93-1.70) (Table 3). It seems that both treatments are equivalent in the prevention of variceal rebleeding with rebleeding rates of 32%-35%^[51].

EVL vs NSBBs and EVL

The combination of NSBBs and EVL is the preferred treatment as it results in lower rebleeding rates compared to each therapy alone. In a recent meta-analysis of nine trials, combination treatment was compared to either EVL (seven RCTs) or a medical therapy alone (three RCTs)^[57]. Random effect analysis showed that combination therapy reduced the risk of overall rebleeding, variceal rebleeding (RR = 0.65, 95%CI: 0.45-0.93), and bleeding-related mortality (RR = 0.52, 95%CI: 0.27-0.99) compared to EVL monotherapy (Table 3). No difference was observed in the overall mortality. When compared to pharmacologic treatment alone, combination with EVL reduced variceal rebleeding (RR = 0.61, 95%CI: 0.44-0.86) and bleeding-related mortality. However, no difference was observed either in overall bleeding (RR = 0.76,

95%CI: 0.56-1.04) or mortality rate (RR = 1.08, 95%CI: 0.73-1.6). Combination therapy increased the risk of serious adverse events in fixed analyses, but not in random effects meta-analyses.

TIPS vs endoscopic treatment

TIPS has greater efficacy in preventing rebleeding than either EVL or sclerotherapy. However, TIPS increases hepatic encephalopathy rates and has no impact on survival. A recent meta-analysis of 12 trials showed significant decreases in the number of variceal rebleedings and in variceal rebleeding-related mortality when using TIPS (OR = 0.35, 95%CI: 0.18-0.67)^[58]. Although TIPS did increase the rate of post-treatment encephalopathy (OR = 2.21, 95%CI: 1.61-3.03), the overall mortality was identical between TIPS and endoscopic treatments (Table 3). However, the above trials have used uncovered TIPS stents. The use of PTFE-covered stents improves TIPS patency and decreases the number of clinical relapses and re-interventions without increasing the risk of encephalopathy^[59]. Therefore, TIPS with PTFE-covered stent is the preferred option and should be used in patients who have failed endoscopic and pharmacologic treatment for the prevention of rebleeding^[9].

A recent meta-analysis of 51 RCTs compared various interventions for secondary prophylaxis of variceal bleeding^[60]. TIPS, beta-blockers combined with sclerotherapy and EVL combined with sclerotherapy were superior to beta-blockers alone in reducing rebleeding probability (ORs = 0.13, 0.23 and 0.13, respectively)^[60]. TIPS treatment was superior to beta-blockers (OR = 0.11), EVL (OR = 0.13), sclerotherapy (OR = 0.19), beta-blockers combined with IsMn (OR = 0.16), and beta-blockers combined with sclerotherapy (OR = 0.14) in regard to bleeding-related mortality. Concerning the overall mortality, beta-blockers combined with IsMn were more effective than either beta-blockers alone (OR = 0.56) or EVL (OR = 0.64). EVL combined with sclerotherapy was the best choice based on the cumulative probabilities, being among the three most efficacious interventions for all three outcomes.

Selective surgical shunts, such as H-graft portacaval shunts and distal splenorenal shunts, have a limited role in the management of portal hypertension. Surgical shunting is used to prevent rebleeding in patients with well-compensated cirrhosis who failed endoscopic and pharmacologic treatment^[9]. This procedure is used in

cases when TIPS is unavailable or is recurrently dysfunctional^[13].

Summary

Current treatment guidelines recommend that secondary prophylaxis of variceal bleeding should include NSBBs combined with EVL. TIPS with covered stents are the preferred option in patients who fail endoscopic and pharmacologic treatment. Surgical shunting is rarely used in cases when TIPS is unavailable.

OTHER ENDOSCOPIC TECHNIQUES IN THE MANAGEMENT OF ESOPHAGEAL VARICES

Argon plasma coagulation (APC) has been used in the management of esophageal varices. A prospective trial randomly assigned patients with esophageal varices to either APC (after EVL) or EVL alone^[61]. The cumulative recurrence-free rate at 24 mo after treatment was significantly higher in the combination group than in the monotherapy group (74.2% *vs* 49.6%). Furthermore, the combination groups also had higher incidence of pyrexia. In another study, groups of 50 patients with esophageal varices each were subjected to sclerotherapy (Group I), EVL (Group II), combined treatment of EVL with sclerotherapy (Group III), or EVL plus APC (Group IV)^[62]. Recurrence rates of esophageal varices were 14% in Group I, 28% in Group II, 2% in Group III, and 4% in Group IV. Higher mortality incidences were detected in Groups I (18%) and II (12%) than in Groups III (8%) and IV (8%). However, APC plus EVL was the most expensive procedure. Contrary to the aforementioned results, a recent RCT showed the additive benefit of APC on variceal recurrence and bleeding was comparable to EVL alone at three and six months of follow-up^[63]. Cipolleta *et al*^[64] studied the efficacy of APC after eradication of varices with EVL in secondary prophylaxis of variceal bleeding, randomizing 16 patients to APC and 14 patients to a control group. In the APC group, there was no recurrence of varices or variceal bleeding during follow-up (mean 16, range 9–28 mo), whereas in the control group, varices and bleeding recurred in 42.8% and 7.2%, respectively.

Tissue adhesives have been used in the management of esophageal varices, as they promote immediate obliteration of the vessel after injection inside the lumen of the varix. In a recent RCT, 38 patients with esophageal varices and Child-Pugh scores of at least eight were randomly assigned to EVL ($n = 20$) or cyanoacrylate injection ($n = 18$) treatment groups^[65]. There were no differences between the groups in variceal eradication rates (90% *vs* 72%, respectively), bleeding episodes until eradication (5% *vs* 22%), mortality (55% *vs* 56%) or major complication rates (5% *vs* 17%). However, a higher incidence of variceal recurrence was observed with cyanoacrylate (33% *vs* 57%). Evrard *et al*^[66] compared endoscopic

n-butyl-cyanoacrylate (NBC) injection ($n = 21$) to propranolol ($n = 20$) in the secondary prophylaxis of variceal bleeding. No difference was observed between NBC and propranolol in terms of six-week rebleeding (23.8% *vs* 15.0%, respectively), bleeding-related mortality (14.3% *vs* 30.0%), long-term rebleeding (52.4% *vs* 25.0%), or overall mortality (42.9% *vs* 45.0%). However, a higher incidence of complications was observed in the NBC group.

Tissue adhesives have also been used in esophageal AVB. In a prospective cohort study of 133 cirrhotic patients with bleeding esophageal varices (52 with active and 81 with recent bleeding), NBC achieved initial hemostasis in 49 (94.2%) patients with active bleeding^[67]. There were low rates of early rebleeding and six-week mortality (5.2% and 8.2%, respectively) without major procedure-related complications. In a recent RCT, comparison of sclerotherapy to NBC injection showed a superiority of NBC in reduction of both rebleeding (11.1% *vs* 55.6%) and mortality rates (33.3% *vs* 72.2%)^[68]. Two RCTs compared the combination of sclerotherapy and NBC to sclerotherapy alone^[69,70]. The combination group resulted in lower rebleeding and mortality rates, and fewer minor complications. In a recent RCT, patients with esophageal AVB were randomly allocated to groups receiving EVL ($n = 21$) or NBC injections ($n = 22$). No differences were observed between the two groups in terms of initial hemostasis or transfusion requirements, or in mortality (NBC: 45.5%; EVL: 33.0%)^[71]. Although patients receiving NBC had a higher rebleeding rate than those receiving ligation (13.6% *vs* 4.7%), the difference was not significant.

Glue embolization is a serious and life-threatening complication following endoscopic glue obliteration of esophagogastric varices^[72]. Coils, delivered under endoscopic ultrasound (EUS) guidance in conjunction with NBC injection, can reduce the risk for glue embolization^[73]. Binmoeller *et al*^[74] treated 30 patients with bleeding gastric fundal varices using transesophageal EUS-guided therapy with combined coil and NBC injection. EUS-guided treatment was successful in all patients, and hemostasis of acute bleeding was similarly achieved in all patients. Among 24 patients with a mean follow-up of 193 d (range: 24–589 d), gastric fundal varices were obliterated after a single treatment session in 23 patients (95.8%). Rebleeding occurred in four patients (16.6%), which was not attributed to gastric varices. There were no procedure-related complications and no symptoms or signs of NBC embolization.

Endoloops are detachable nylon snares that were proposed to treat esophageal varices as an alternative treatment to EVL. However, there have been no RCTs comparing endoloop efficacy with that of EVL. In a prospective non-randomized study, 25 patients with AVB were treated with elastic band ligation and 25 with endoloop ligation^[75]. The rate of rebleeding during a 6-mo follow-up was lower with endoloops (12%) than with band ligation (28%), but without statistical significance. In addition, no differences were found between the two

groups in terms of variceal eradication, number of treatment sessions for variceal eradication, or variceal recurrence.

Endoscopic clipping of esophageal varices has also been proposed as an alternative in variceal obliteration. In a prospective non-randomized study, 19 patients with AVB were treated with endoscopic clipping and 21 with band ligation^[76]. Initial hemostasis was achieved in all patients treated with clipping and in all but two patients treated with banding. There was no difference between the treatments regarding variceal eradication (clipping: 89% and ligation: 76% of patients) and rebleeding rates (15% *vs* 33%). However, the median number of sessions needed for variceal eradication was lower with clipping than with band ligation (3 *vs* 4). These results suggest that clipping is as efficacious as banding ligation, but this observation needs to be tested in large RCTs.

The data on the efficacy and safety of laser treatment in AVB are scarce. In an old RCT, endoscopic laser treatment ($n = 10$) was compared with sham endoscopy and standard medical treatment ($n = 10$)^[77]. Initial hemostasis was achieved in seven laser-treated patients, but four of them rebled 12 to 48 h later. None of the controls achieved initial bleeding control. There was no difference with regard to in-hospital mortality between groups (laser: 40%; controls: 70%).

de Paulo *et al.*^[78] aimed to compare endoscopic sclerotherapy ($n = 25$) of esophageal varices with EUS-guided sclerotherapy of esophageal collateral veins ($n = 25$). EUS-sclerotherapy was found to be as safe and effective as sclerotherapy in variceal eradication, whereas recurrences tended to be less frequent and occurred later. Lastly, in a small RCT, endoscopic treatment with human-derived fibrin glue was found to be superior to sclerotherapy in terms of rebleeding, mortality, and incidence of complication^[79].

Percutaneous transhepatic variceal embolization (PTVE) of gastroesophageal varices has been used in AVB, but has been abandoned due to the high incidence of variceal recurrence and rebleeding^[80]. An RCT including 102 cirrhotic patients with acute or recent esophageal variceal bleeding compared treatment with a modified PTVE with 2-octyl cyanoacrylate (2-OCA) ($n = 52$) to EVL ($n = 50$) for the eradication of esophageal varices through the portal vein^[81]. With modified PTVE, 2-OCA was injected into the whole lower esophageal and paraesophageal varices, and into the submucosal varices and the adventitial plexus of the cardia and fundus. During follow-up, upper gastrointestinal bleeding developed in eight patients in the PTVE group and 21 patients in the EVL group. Recurrent bleeding from esophageal varices occurred in three patients in the PTVE group and 12 in the EVL group (RR = 0.24, 95%CI: 0.05-0.74). However, there was no difference in the survival between groups. Studies with larger populations are needed to confirm the efficacy of these alternative endoscopic techniques, considering the safety issues that accompany their use.

COMPLICATIONS OF ENDOSCOPIC TECHNIQUES

EGD safety

The number of complications associated with emergency cases of diagnostic EGD increases from 0.7% to 8.0%, with the majority of incidences being cardiopulmonary^[82]. Aspiration can occur in approximately 2.4% of patients with index bleeding and 3.3% in cases of rebleeding^[83]. In a retrospective study, 42 patients with AVB who underwent elective intubation were compared to 20 patients without intubation^[82]. Pulmonary infiltrates developed in seven (17.2%) intubated patients, but not in the non-intubated patients. Evaluation of prophylactic endotracheal intubation in intensive care unit patients with upper gastrointestinal bleeding prior to endoscopy showed no difference in the number of EGD-related cardiopulmonary complications, new pulmonary infiltrates, mean number of ICU days, or mortality^[84]. The issue of elective intubation prior to endoscopy remains debatable.

Sclerotherapy

Endoscopic variceal eradication by sclerotherapy has been associated with esophagus motility abnormalities and gastroesophageal reflux, though the exact mechanism is not well understood^[85,86]. These disturbances have not been observed when using EVL. Comparison of sclerotherapy to EVL in the AVB setting has also been associated with a greater incidence of transient bacteremia (17.2% *vs* 3.3%) and infectious complications (18.0% *vs* 1.8%), such as spontaneous bacterial peritonitis and distant abscesses^[87]. Sclerotherapy-associated cardiopulmonary complications include pericarditis, pleural effusions and acute respiratory distress syndrome^[88]. Additional adverse events associated with sclerotherapy include esophageal ulcers, with the probability of bleeding and esophageal stenosis following a long-term treatment^[87]. Esophageal perforation is a rare life-threatening complication that can occur in cases of traumatic rupture during the procedure or in cases of necrosis of the esophageal wall.

EVL

EVL is associated with retrosternal pain, transient dysphagia, or pyrexia^[89]. Prior to the development of multi-band ligators, the required repeated reinsertion of the device into the esophagus was associated with esophageal tears and perforation^[90,91]. With an increased need for a double intubation, the risk for aspiration increases as well^[92]. Post-banding esophageal strictures occur at a rate of 1.9%^[93]. EVL-related esophageal ulcers are commonly found endoscopically, however, they tend to be more superficial compared to sclerotherapy-related ulcers^[94,95]. Iatrogenic bleeding has raised the issue of EVL safety, especially in the setting of primary prophylaxis of variceal bleeding^[17,27,96,97]. A recent study showed that 3.5% of patients develop post-banding bleeding following EVL treatment^[98]. The multivariate analysis showed that previ-

ous variceal bleeding (OR = 12.07, 95%CI: 2.3-63.43), peptic esophagitis (OR = 8.9, 95%CI: 1.65-47.8), high platelet ratio index score (OR = 1.54, 95%CI: 1.11-2.16) and low prothrombin index (OR = 0.54, 95%CI: 0.31-0.94) were independent predictive factors of post-banding bleeding occurrence^[98]. Some studies showed an increased risk of developing or worsening pre-existing portal hypertensive gastropathy, as well as formation of fundal varices following EVL, however, this observation has not been confirmed by others^[99,100]. The main drawback of multi-band ligators is the limited endoscopic field of view^[91].

CONCLUSION

Endoscopic treatment is the standard of care in the management and prophylaxis of variceal bleeding in patients with liver cirrhosis. The treatment leads to improved survival rate, though in Child-Pugh C patients, mortality still remains > 30%. There are safety issues accompanying endoscopic techniques in primary and secondary prophylaxis, and in AVB. Thus, there is still a need for future research to improve treatment strategies, including novel endoscopic techniques, with better efficacy, lower cost, and fewer adverse events.

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