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Current Approaches to Esophageal Variceal Bleeding

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Abstract
Esophageal varices are collateral veins at the distal esophagus between gastric and azygos veins arising following increased portal pressure. Vein pressure above 10 mmHg is regarded as portal hypertension, in which portal vein-hepatic vein pressure gradient is increased. This status is seen as "clinically important portal hypertension" and it is most common in liver cirrhosis. Acid and esophageal variceal bleeding is the result of portal hypertension, which are the signs of advanced disease with poorer survival rates. Esophageal varices develop in 30% of the patients with compensated cirrhosis and 60-70% of the patients with decompensated cirrhosis. Varice development incidence is around 4-12% in cirrhotic patients without varices. Esophageal variceal hemorrhage has high recurrence, mortality, and morbidity rates requiring immediate medical treatment and these constitute approximately 10% of upper gastrointestinal bleeding, which is one of the major causes of mortality in patients with cirrhosis. Bleeding develops in 30% of the cirrhotic patients with esophageal varices diagnosed during endoscopy. The mortality of the first bleeding episode ranges from 25 to 70% and after the first bleeding episode re-bleeding occurs at a rate of 75-80% in six to twelve months. Variceal diameter, grade, degree of red dots, and cirrhosis are among the factors that increase the risk of variceal bleeding. The risk of bleeding in Grade 1 varices is 8% and a higher grade increases the risk of bleeding four to five folds. Pharmacological endoscopic and antibiotic treatment constitutes the basis for esophageal variceal bleeding treatment. In this study, we aimed to evaluate the current approaches to esophageal variceal bleeding.
Key Words: Esophageal Variceal Bleeding; Portal Hypertension; Cirrhosis.

Özofagus Varis Kanamalarına Güncel Yaklaşımlar

Özet
Özofagus varisleri portal kan basıncının artmasına bağlı, özofagusun distalinde gastrik venler ile azigos ven arasında geşilen kolaterallerdir. Portal ven basıncının 10 mm Hg'nin üzerinde olmasına portal hipertansiyon denilir. Portal hipertansiyonda portal ven – hepatik ven basınç gradiyenti artmıştır. Bu durum "klinik olarak önem arz eden portal hipertansiyon" olarak adlandırılmaktadır ve en sık karaciğer sirozunda karşılaşılır. Karaciğer sirozu olan hastalarda asit oluşumu ve özofagus varis kanamalarının olması ilerlemiş hastalık belirtileridir ve bu hastaların beklenen yaşama süresi oldukça kısalmıştır. Kompanze sirozlu hastaların %30'unda dekompanze sirozlu hastaların %60-70'inde özofagus varisi gelişmektedir. Varisi olmayan sirotik hastalarda yıllık varis oluşum hızı %4-12 dolayındadır. Özofagus varis kanaması yüksek rekürrens, mortalite ve morbidite oranına sahip acil medikal tedavi gerektiren hastalıklardan biridir. Özofagus varis kanamaları üst gastrointestinal sistem kanamalarının yaklaşık %10'unu oluştururlar ve sirozlu hastalarda başlıca mortalite nedenlerindendir. Özofagus varis kanaması, endoskopik olarak özofagus varisi saptanan sirotik hastaların %30'unda gelişmektedir. İlk kanama epizodunun mortalitesi % 25-70 arasında değişmektedir ve ilk kanama sonrası varislerin % 75-80'inde altı ay ya da bir yıl içinde yeniden kanama meydana gelir. Varis çapı, grade, kırmızı noktalanmalar ve siroz derecesi varis kanaması riskini arttıran faktörlerdir. Grade 1 varislerde kanama riski %8 iken grade arttıkça kanama riski 4-5 kat artmaktadır. Özofagus varis kanamalarında tedavinin temelini farmakolojik, endoskopik ve antibiyotik tedavisi oluşturur. Bu çalışmada özofagus varis kanamalarına güncel yaklaşımlar ele alınmıştır.
Anahtar Kelimeler: Özofagus Varis Kanaması; Portal Hipertansiyon; Siroz.

Esophageal variceal bleeding occurs in enlarged submucosal veins due to esophageal shunts as a result of portal hypertension (PHT).

Pathophysiology

PHT is defined as the increase in blood pressure in the portal venous system. Portal pressure can be indirectly estimated by hepatic venous gradient. Normal hepatic venous pressure gradient is less than 5 mmHg. In cirrhosis, in the context of Ohm's law (Pressure= vascular resistance X blood stream), patients may develop increased intrahepatic vascular resistance and PHT due to the blood stream flowing towards portal venous system (Figure 1).

Intrahepatic resistance is increased in two ways: mechanical and dynamic. The mechanic component is connected to development of intrahepatic fibrosis. Whereas, the dynamic component occurs due to the induced vasoconstriction in the portal veins. Intrehepatic vascular tonus is regulated by endogenous vasoconstrictors such as norepinephrine, endothelin-1, angiotensin-2, thromboxane, leukotrienes as well as vasodilators such as nitric oxide. PHT, which leads to acid and variceal bleeding in cirrhosis, is caused by the deterioration of the balance between these vasoconstrictors and vasodilators (1-3).

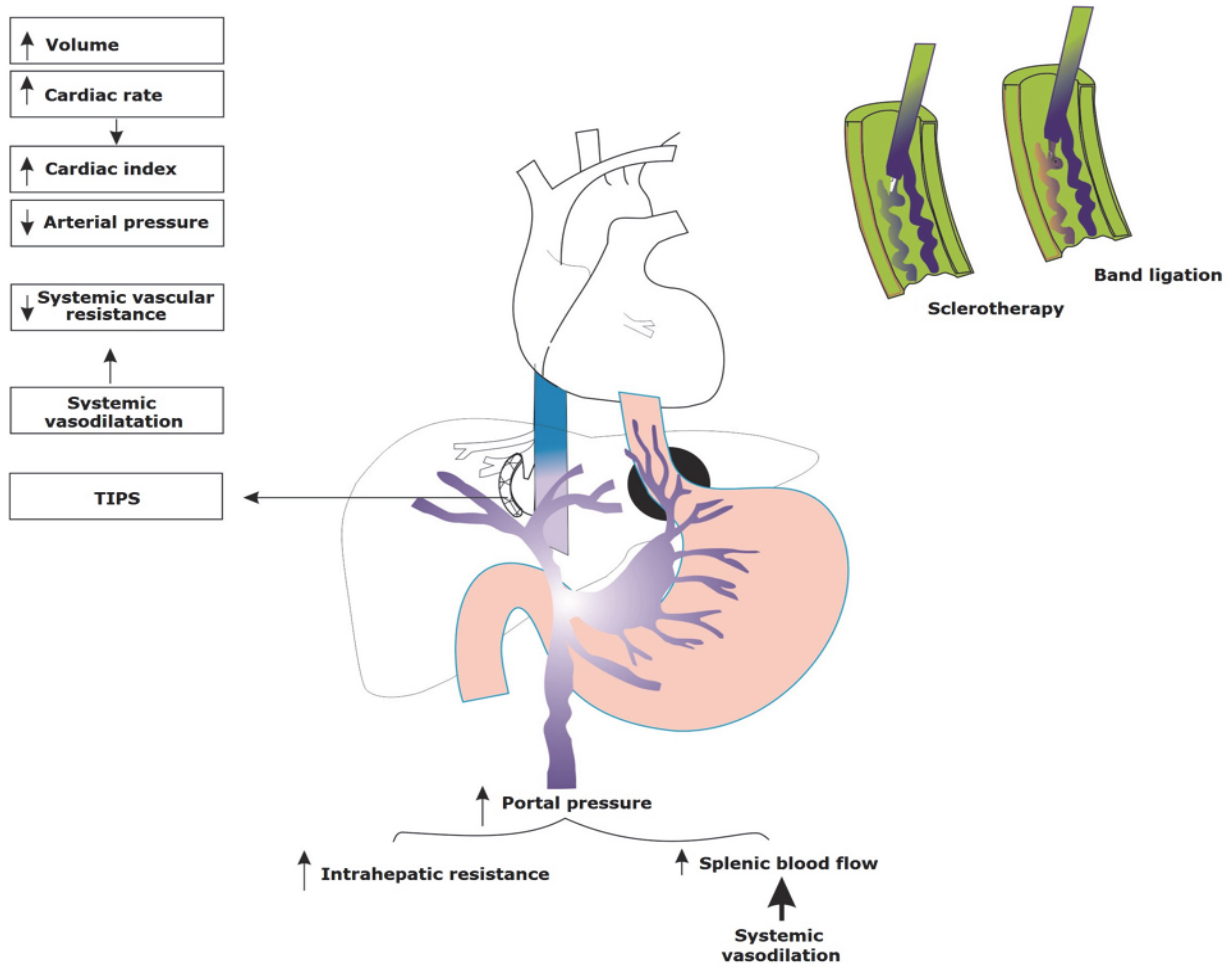

Figure 1. The pathophysiology of portal hypertension; based on Nina D. et al.'s diagram (1).

PHT is characterized by hyperdynamic circulation resulting from splanchnic and systemic arterial vasodilation, and, in turn, increased cardiac outflow and decreased systemic vascular resistance. Splanchnic arterial dilatation develops due to endogenous vasodilators such as glucagon and vasoactive intestinal peptides and it leads to increased portal blood flow. The emerging PHT creates portacaval pressure difference. Hence, portosystemic venous collaterals develop in order to try to reduce this pressure difference. Esophageal varices generally drain down to azygos veins and they are considered to be one of the most important collaterals due to their tendency to bleed. Esophageal varices develop when the hepatic venous pressure difference exceeds 10mmHg (4). All the factors such as deterioration in liver disease, patient's diet, ethanol intake, physical execise, and increased intra-abdominal pressure that contribute to high PHT values increase variceal bleeding and acid formation (5, 6). Aspirin and non-steroidal anti-inflammatory drugs may increase the tendency for bleeding by changing the variceal wall structure. In addition, bacterial infections may also be effective on the formation of varices and the risk of bleeding.

Esophageal Variceal Bleeding

Variceal bleeding has been one of the diseases with high risk of recurrence, mortality, and morbidity rates and it requires urgent medical treatment. The prevalence of varicose veinin cirrhotic patients is about 50%. In the presence of PHT, annual growth rate of varicose vein is between 4 and 12 %. Pharmacological, endoscopic, and antibiotic treatment form the basis of varicose vein treatment. Endoscopy is the most valuable diagnostic method. Varicose vein observed in endoscopy are generally classified in three grades.

- Grade 1: Observed in a single column; disappearing air application; depressed by endoscopy.
- Grade 2: Observed in more than one columns; cannot be depressed by fluid resuscitation or endoscopy.

- Grade 3: Multiple intercorrelated varicosis; occupying more than 2/3 of the lumen space; cannot be depressed by giving air or endoscopy

Varicose diameter, grade, red dots, and degree of cirrhosis are factors that increase the risk of variceal bleeding. In grade 1 varices, the risk of bleeding is 8 %, but as the grade increases, the risk of bleeding also increases up to 4-5 times. 30-35% of chronic liver of patients with varicose veins bleed within 2 years and they share a mortality rate of about 30-50 %.

Gastroesophageal Varicose Veins

Endoscopic screening is the best technique; today there is no other technique indicating the presence of esophagogastric varices than endoscopic screening. In patients with esophageal varices, prevalence of gastric varices is also high. Gastroesophageal varices are divided into 2 groups:

Type 1: This is the most common type of esophageal varices. They can be 2-5 cm below the cardio-esophageal junction. The risk of bleeding is about 12%, which is less than the bleeding percentage in other types.

Type 2: They are the varices that spread towards the fundus. They have two subgroups. The first subgroup only occupies the fundus (with a bleeding risk of 80%, the highest bleeding risk among varicose veins) while the other group spreads over the antrum and corpus.

Pharmacological Treatment

Vasopressin/Terlipressin: Vasopressin is a potent splanchnic vasoconstrictor agent. In many countries, it has been discontinued due to its severe vascular side effects. Terlipressin, however, is the equivalent of vasopressin and it reduces hepatic venous pressure gradient, variceal pressure, and azygos blood flow by showing similar effects as vasopressin. Terlipressin has been proven to reduce variceal bleeding compared to placebo. In addition, it protects the renal function of patients with hepatorenal syndrome by reducing the activation of renal vasoconstrictor system. However, terlipressin may increase ischemic complications in patients who are in shock. Therefore, the use of this drug in patients with cardiovascular diseases such as heart failure, arrhythmia and hypertension is contraindicated (7, 8).

Somatostatin, Octerotid, Vapreotide: Somatostatin reduces the hepatic venous pressure gradient, variceal intraocular pressure, and azygos blood flow. However, its hemodynamic effects are temporary and require continuous infusion. Also, information on the idea that it reduces the need for blood transfusion and balloon tamponade is controversial. Terlipressin is as as effective as somatostatin in bleeding control. Octreotide and vapreotide have longer half-life than somatostatin and they are more useful in the treatment of PHT. Octreotide reduces the hepatic venous pressure gradient and azygos blood flow but does not affect the varices pressure. Moreover, the effect of octreotide is temporary and even this effect is controversial. It prevents the postprandial increase in hepatic blood flow while it also seems to reduce variceal bleeding and increase the success of endoscopic treatment (1, 7, 9, 10). Published randomized controlled studies show that Octreotide is not more effective than placebo in the prevention and control of variceal bleeding (11). Some studies also show that vapreotide, which is a long-acting counterpart of somatostatin, reduces the need for blood transfusion when it is given before endoscopic treatment; besides, it is only found to be more effective than the group treated by endoscopy (12). With regard to the use of somatostatin and its counterpart drugs, there is almost no major complications and toxic effects.

Endoscopic Treatment:

In variceal bleeding, endoscopy is a commonly used technique in both the diagnosis and treatment of the bleeding. Three types of endoscopic techniques are commonly used: Endoscopic band ligation, sclerotherapy, and endoscopic variceal occlusion by using adhesives.

Endoscopic band ligation: Today, it is the first choice for esophageal variceal hemorrhage. Only up to 5-8 tapes should be used in every session. Sessions should be implemented with intervals of 2-3 weeks until varices are entirely obliterated or shrunk. Endoscopic band ligation is a relatively less complicated operation compared to sclerotherapy. After ligation, occasional moderate bleeding can be observed due to ulcer developing in the area.

Endoscopic Sclerotherapy: There are several sclerosing agents such as polydocanol, ethanolamine, ethanol, tetradecyl sulfate, and sodium morruat. The effects of these agents are similar. In each session, an injection of sclerosing with total volume of 10-30 ml can be administered inside or around the varices. Sessions continue with intervals of 1-3 weeks until varices are obliterated. Thereafter, since the probability of re-occurrence of the varices is up to 70 %, endoscopic follow-ups are required with intervals of 3-6 months. Retrosternal pain, dysphagia, and sclerotherapy related ulcer bleeding can be observed due to sclerotherapy. Esophageal perforation and stricture due to sclerotherapy may also develop though this is quite rare.

Variceal Obliteration by using Adhesives: This treatment is more suitable for patients who have suffered from gastric or gastroesophageal variceal bleeding in the past. Generally, practitioners use N-butyl-2-cyanoacrylate in this method. 1 ml adhesive is injected at one time and only up to 3 injections are implemented in each session. The most serious complication of this treatment is the possibility of embolization in the pulmonary system, spleen, and the brain.

Transjugular Intrahepatic Portosystemic Shunt (TIPS):

TIPS refers to providing a new path between the hepatic and portal vein via jugular vein in the liver (Figure 1). Here, the purpose is to prevent variceal bleeding by reducing portal pressure. TIPS reduces portal pressure,

but there is a risk of encephalopathy. In most cases, encephalopathy responds to standard treatments but in some cases, it may be neccessary to reduce the diameter of the shunt. 5% of encephalopathy patients do not respond to treatment; in this case, practitioners need to stop the flow in the shunt. In addition, from time to time, stenosis or thrombosis may develop in the shunt. In recent years, there are studies that report that stents wrapped with polyether urethanes tend to get clogges less than conventional stents.

Other Treatment Options:

Balloon tamponade: Balloon tamponade is a bridging therapy for TIPS and portosystemic shunts in cases with massive and uncontrolled bleeding. The most frequently used tube is the modified 4-lumen Sengstaken-Blakemore tube. In gastric varices, practitioners prefer Linton-Nachlas tube which has a wider lumen.

Porto-Systemic Shunt: After the introduction of TIPS, the use of surgical shunts has dramatically decreased. The implementation of surgical shunts are complicated operations that require experience. This method can be useful in patients for whom TIPS is technically impossible and when the liver functions of the patient are not severely decreased.

If the bleeding is still unstoppable despite all attempts, procedures such as percutaneous transhepatic embolisation, devascularization-transection, or transplantation can be considered as last resources.

Practical Treatments:

Variceal bleeding should be treated in intensive care units. The treatment can include nonspecific treatment options like fluid replacement or antibiotic treatment therapies as well as patient-specific methods like pharmacological and endoscopic treatments (Figures 2, 3).

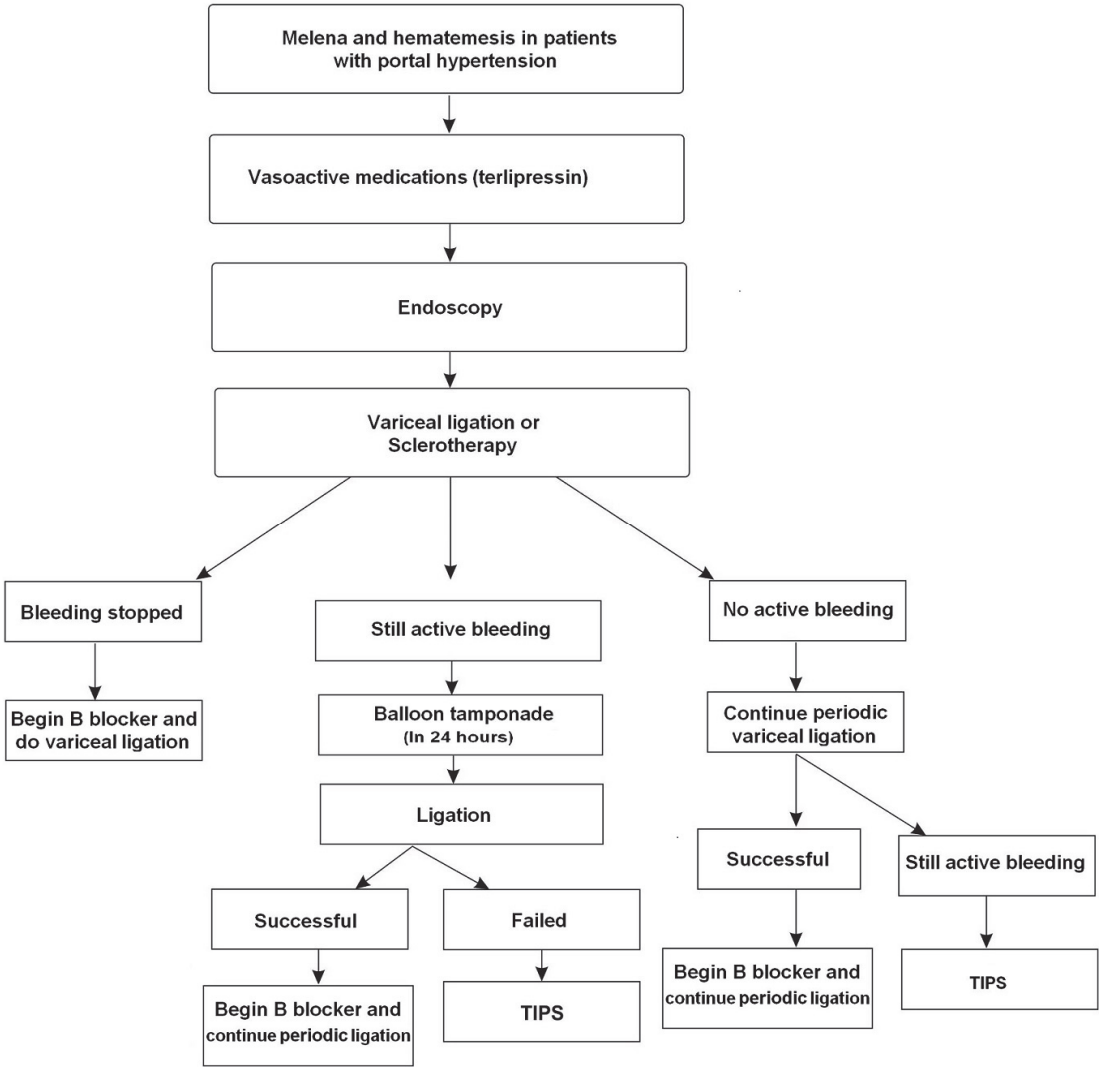

Figure 2. Approach algorithm for patients with active esophageal variceal bleeding.

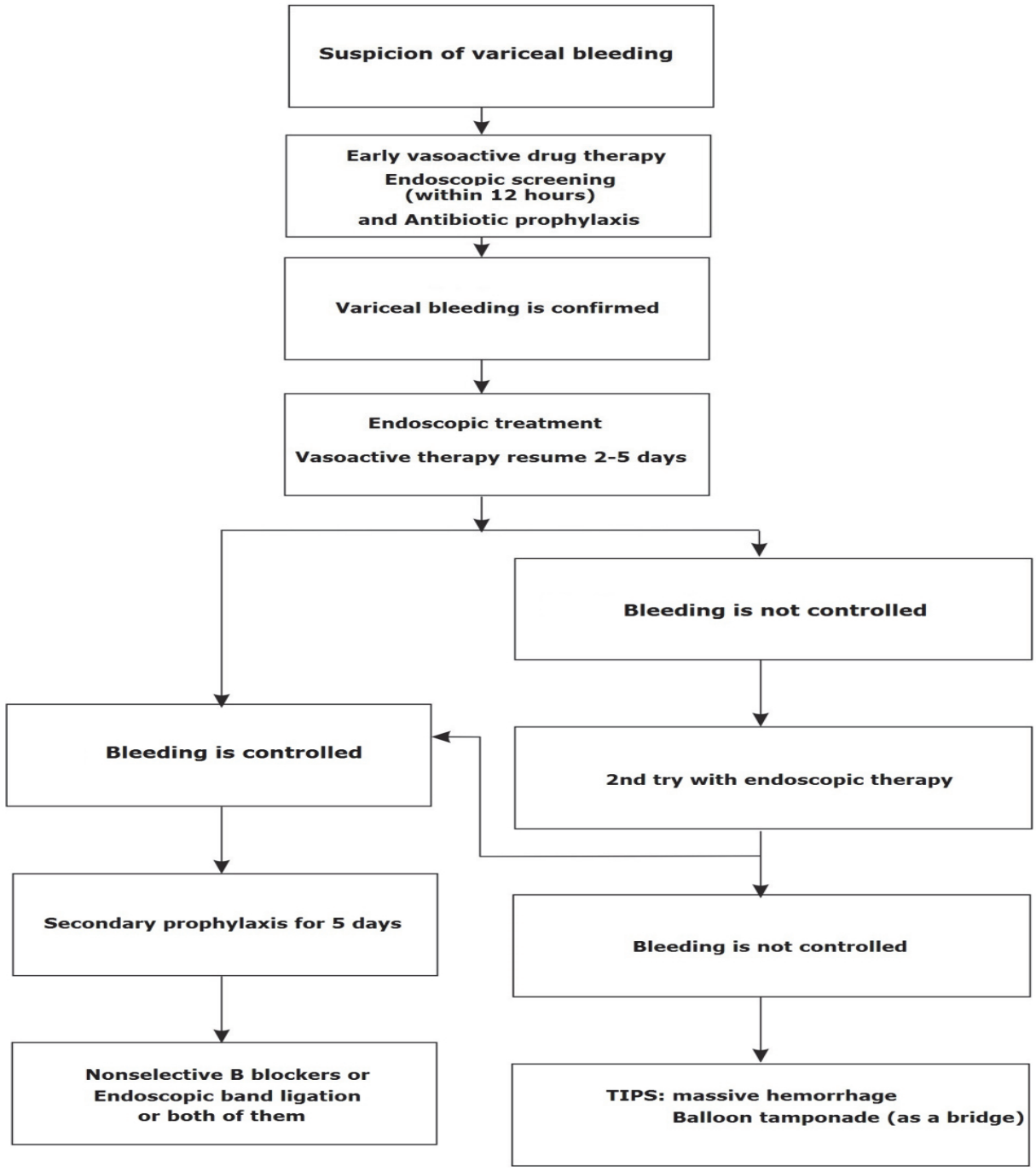

Figure 3. Approach algorithm for patients with variceal bleeding.

Practical Recommendations for the treatment of acute variceal bleeding (1):

-Variceal bleeding is medically an emergency case and must be treated in intensive care units.
-Blood replacement should be carried out carefully.
-Red blood cells should be maintained at a hemoglobin level of 70 to 80 g/L.
-Plasma expanders should be used for hemodynamic stability and renal perfusion.
-Antibiotic prophylaxis
-Endoscopic treatment should be given as quickly as possible (within the first 12 hours of admission to hospital).

-Treatment should include vasoactive drugs along with endoscopic therapy and a specific treatment.
1) One of the following drugs should be started as soon as possible immediately after admission to the hospital prior to endoscopic treatment (to be administered for the first 2-5 days):
-Terlipressin: 1-2 mg every 4 hours
-Somatostatin: 250µg bolus; then 250µg infusion therapy every hour
-Octreotide: 25-50µg/h infusion and 50-100µg bolus if required
-Vapreotide: 50 mg bolus and 50 mg/h infusion.
2) If possible, practitioners should first consider endoscopic band ligation or endoscopic sclerotherapy. Tissue adhesives can be applied in acute gastric variceal bleeding (such as N-butyl-2-cyanoacrylate)
-Should vasoactive drugs and endoscopic treatment fall short, endoscopic treatments or TIPS can be reapplied.

Nonspecific treatment:

The purpose of the non-specific treatment is to correct hypovolemia and prevent complications. Blood replacement should be applied with erythrocyte suspension by keeping the hemoglobin level at 70-80 g/L. Practitioners should avoid over transfusion which brings about recurrent bleeding and increases the risk of continuous bleeding (14). Plasma expanders are used to maintain hemodynamic stability and renal perfusion pressure. To this end, either crystalloids or colloids can be preferred but it should also be kept in mind that crystalloids are known to be less harmful.

25-50% of the patients may develop infections in cirrhosis related esophageal variceal bleeding. Controlling bleeding is difficult in infected patients; death rate is higher in such cases. Early antibiotic prophylaxis is beneficial both for survival and bleeding control. The preferred protocol is generally the application of 400mg of norfloxacin twice a day for two weeks (15).

The routine nasogastric tube application is not recommended at this stage. Although we do not know for sure if lactulose prevents encephalopathy, practitioners are recommended to apply lactulose in encephalopathic patients (16).

Specific Treatment

Intravenous vasoactive medications should be started right after admission to the hospital and maintained for 2-5 days. Due to its possible side effects, vasopressin is not recommended for routine applications. Endoscopy should be scheduled within 12 hours of admission. For this, stomach should be emptied - if needed, with a nasogastric tube. It is useful to apply 250mg of intravenous erythromycin 30-60 minutes before the procedure (1).

Endoscopy is highly beneficial in locating and treating the source of bleeding. The first step could be to achieve homeostasis with the help of band ligation or sclerotherapy. In patients with gastric or gastroesophageal variceal bleeding, N-butyl-2-cyanoacrylate and endoscopic obliteration should be preferred. Band ligation can also be administered in patients with gastroesophageal reflux. Should vasoactive and endoscopic treatments prove to be insufficient for the treatment, practitioners may try a second endoscopic intervention. It should be remembered that TIPS is a method that should be considered in the second step of the procedure.Balloon tamponade can also be applied as a bridging treatment against massive bleeding. TIPS and surgical shunt operations can be applied as life-saving treatments if bleeding does not stop or gets complicated despite all these preventive approaches (1, 16).

The effects of various methods for variceal bleeding on portal flow, resistance, and pressure are given in Table 1.

Table1. The effects of various methods for variceal bleeding on portal flow, resistance, and pressure.

Treatment	Portal Flow	Portal Resistance	Portal Pressure
Vasoconstrictors	↓↓	↑	↓
Vasodilators	↓	↓	↓
Endoscopic Treatments	--	--	--
TIPS/Surgical shunt	↑	↓↓↓	↓↓↓

Prophylactic Approaches (Figure 4):

There are three main to prevent variceal bleeding:

- By obstructing variceal development (pre-primary prophylaxis),
- By preventing bleeding when the varice develops (primary prophylaxis),
- By preventing recurrent bleeding (secondary prophylaxis).

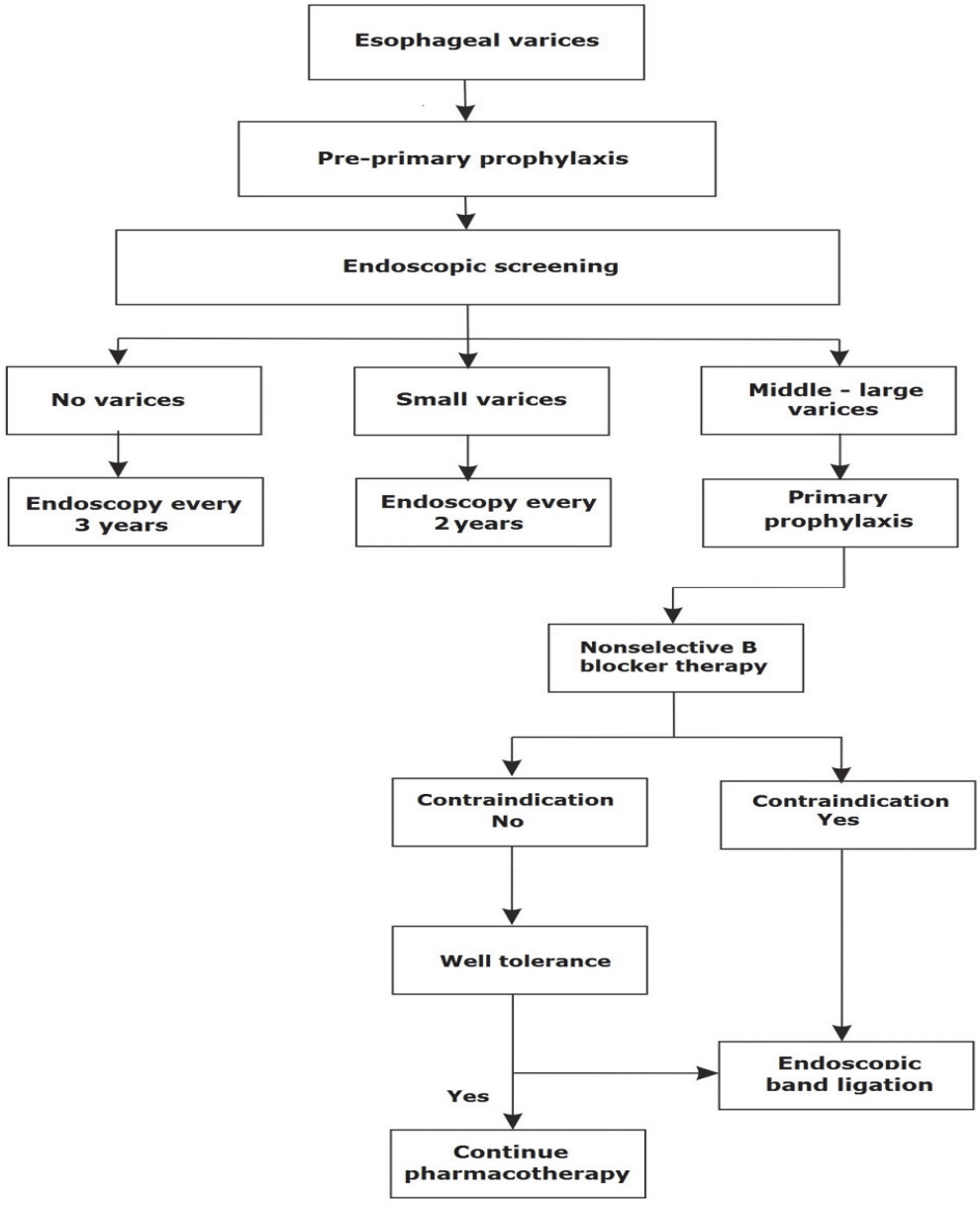

Figure 4. Prophylactic approach algorithm.

Pharmacological Treatment:

Pharmacological agents can be used both for treatment and prophylaxis.

β-blockers: They reduce portal pressure by reducing portal blood flow. Decrease in portal blood flow is caused by the decrease in the cardiac output due to β1 blockage and to the arteriolar splanchnic vasoconstriction that results from the reaction of the alpha receptors against β2 receptor blockage. Nonselective beta-blockers like propranolol, nadolol, and timolol are better than selective beta1 blockers in reducing hepatic venous pressure gradient. Up to a 15% drop can be achieved with nonselective beta-blockers in hepatic venous pressure gradient (17). Nonselective beta blockers may help reduce the volume of bleeding if not provide a significant reduction in hepatic venous gradient by reducing intra-varice pressure and azygos blood flow. It has been reported that using propranolol in cirrhotic patients prevents increase in physical activity related portal pressure while also mitigating bacterial translocation. Although it is still arguable, propranolol is also thought to be effective in reducing postprandial portal pressure peaks. The effect of treatment with beta-blockers can be measured by measuring hepatic venous pressure gradient. Many studies have shown that gradient below 12mmHg or 20% of the base value is considered to be a sign of the absence of variceal hemorrhage (18). However, the impact of hepatic

venous pressure gradient on the survival is controversial. Moreover, some researchers also think that gradient measurement is not cost-effective because it is an invasive method that can be applied only in some centers as a clinical practice (19, 20).

Nitrates: The vasodilator influence of nitrates (reduction in vascular tonus and intra-hepatic resistance) is not fully understood yet. It is probable that it may be effective through nitric oxide release. Isosorbide monohydrate is the only nitrate that is reported to be effective in randomized trials (21). It reduces the hepatic venous pressure gradient while also increasing the impact of propranolol. However, it should be known that isosorbide monohydrate has systemic effects such as hypotension. Nitrates may be used along with vasopressin and its analogous drug, terlipressin.

Pre-Primary Prophylaxis

The results of the studies on this issue are not compatible with one another. The International Baveno consensus recommends that beta-blockers should not be used in primary prophylaxis (22).

Primary Prophylaxis

After the diagnosis of cirrhosis, endoscopic variceal screening should be applied within 3 years in patients without varicose veins and within 2 years in patients with minor varicose veins. The following check-ups should be planned according to the initial size of varicose veins. Endoscopic follow-up is not necessary in patients with large varicose veins; practitioners should start primary prophylaxis with propranolol or nadolol for these patients. Endoscopic variceal band ligation may be considered in medium to large size varicose veins in primary prophylaxis though there is still no clear information regarding the long-term benefits of this application. Therefore, for now, band ligation is only recommended in primary prophylaxis if there are potential issues concerning the use of nonselective beta-blockers. In patients with medium and large size varicose veins, treatment involving nonselective beta-blockers reduces the frequency of the first bleeding episodes. Nonselective beta-blockers are traditionally administered twice a day whereas doses may be modified according to patient's tolerance. Recent pharmacodynamic studies imply that applying 80-160mg of propranolol has a long-acting effect and, thus, this can be sufficient in daily single doses. In all cases, the aim should be to achieve 20-25% reduction in heart rate with a heart rate of 55 beats/min. The use of isosorbide monohydrate alone is not effective in the prophylaxis of variceal occlusion and is not recommended (23).

Recommendations for the primary prophylaxis of variceal bleeding (1, 16):

1. Endoscopic variceal screening should follow the diagnosis of cirrhosis in all patients. Proceeding follow-ups should be scheduled by the degree of liver dysfunction and the size of varices.
2. Nonselective beta-blockers may be initially used in medium or large varicose veins. Treatment should be adjusted according to patient's needs and tolerance. In this group of patients, if the use of beta-blockers brings about contraindication and patient finds it hard to tolerate the therapy, endoscopic band ligation can be initiated.
3. Nonselective beta-blockers can be useful in patients with red, small size varicose veins or Child-Pugh C.
4. General dosage for beta blockers is as follows: propranolol 80-160mg/dl, nadolol 80 mg/dl.
5. Beta-blocker dose should be set to cause a 20-25% decrease in the heart rate to maintain it at 55 beats/min.

Secondary prophylaxis (Figure 5):

All patients who survived the first episode of bleeding should receive treatment for possible secondary bleeding. Risk factors for recurrent bleeding are summarised in Table 2. For the first step of treatment in the prophylaxis for recurrent bleeding, practitioners often employ both pharmacological and endoscopic therapies. Pharmacological treatment consists of nonselective beta-blockers; at this point, practitioners are advised to initiate an isosorbide monohydrate-proparanolol combination but this is not usually regarded as a favourable option. Endoscopic therapy for the treatment of varicose veins is one of the effective ways of treatment to cure recurrent bleeding. Compared with placebo, endoscopic sclerotherapy alone provides significant improvement in mortality rates and recurrent bleeding (22). Today, since it can reduce the risk of recurrent bleeding and due to its advantage to decrease varicose vein structure formation, band ligation is preferred to sclerotherapy. Administrating band ligation and sclerotherapy at the same time has not proved to be more effective than band ligation alone (24). However sclerotherapy may be preferred to band ligation if the patient's case is unsuitable for the latter. Endoscopic band ligation has been reported to be more effective in the prophylaxis of recurrent haemorrhage after a nadolol and sucralfate combination administration (25). As of now, we do not have sufficient data about the effect of the administration of this combination alongside with sclerotherapy. If nonselective beta-blocker and/or band ligation treatments fail in the secondary prophylaxis, salvage therapy options should be considered. Both TIPS and surgical shunts are efficacious in the prevention of recurrent bleeding. While TIPS is more effective than endoscopic treatments, surgical shunts are also more effectual than endoscopic sclerotherapy. Unfortunately, the impact of neither TIPS nor surgical shunts on survival is clear and both pose a risk to encephalopathy (26, 27).

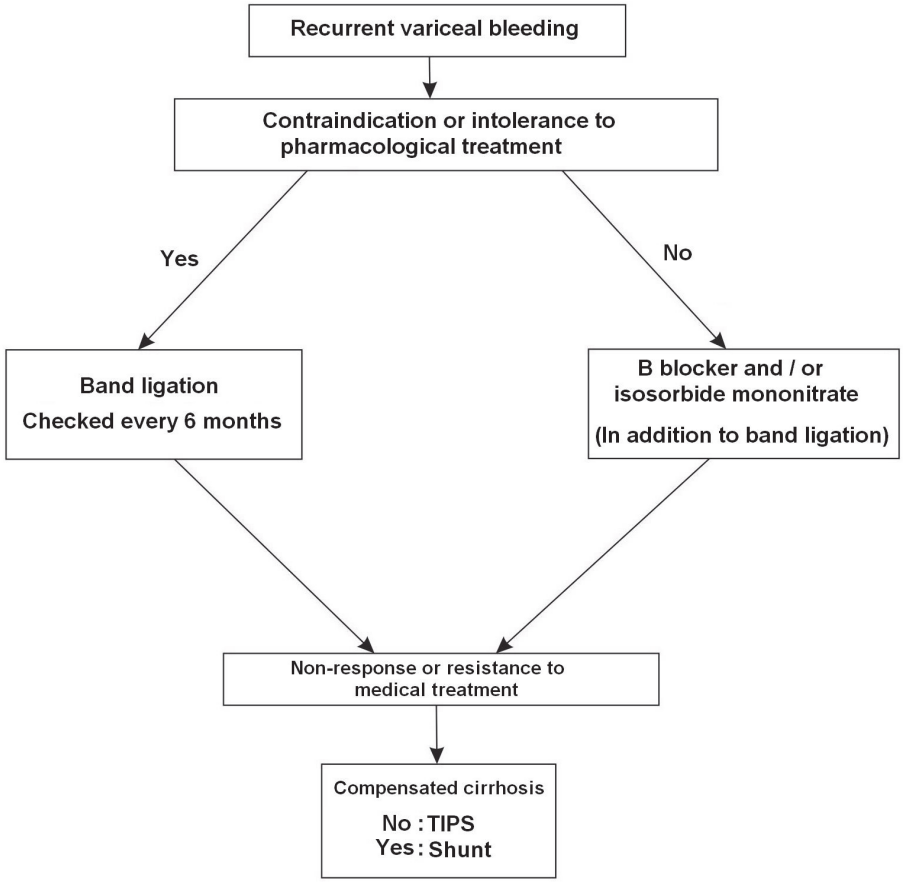

Figure 5. Approach algorithm for recurrent variceal bleeding.

Table 2. Risk factors for recurrent variceal bleeding.

Early recurrence of bleeding (within 6 weeks)	Late recurrence of bleeding (after 6 weeks)
Age (>60)	Cirrhosis Grade
Severe initial bleeding	Red-spotted varicose veins
Acid	Acid
Renal failure	Hepatoma
Identifying active bleeding in endoscopy	Alcoholism
Red-spotted varicose veins and clogs	

Recommendations for secondary prophylaxis (1, 16, 22):
-For patients who do not receive primary prophylaxis, practitioners should opt for nonselective beta-blockers and/or endoscopic band ligation.
-For patients who receive beta-blockers in the primary prophylaxis, practitioners should check whether patients have been administered appropriate doses.
-If the doses are sufficient, practitioners should add band ligation to beta-blocker therapy.
-If the doses are not at intended levels, practitioners should adjust the dose though they may still need to apply band ligation.
-If there are contraindications to beta-blockers or patients cannot tolerate the doses, practitioners should then apply band ligation.
-If band ligation falls short in primary prophylaxis, practitioners should perform TIPS. For all patients with Child-Pugh B-C in particular, liver transplantation should be considered.

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