Review Article

PORTAL HYPERTENSION IN THE LIVER CIRRHOSIS: PHYSIOPATHOLOGY AND THERAPEUTICAL APPROACH OF ESOPHAGEAL VARICEAL BLEEDING

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Abstract

Portal hypertension represent the major consequence of liver cirrhosis, with life-threatening complications like upper digestive hemorrhage through esophageal varices efraction. The physiopathology of portal hypertension in chronic liver disease is dominated by two factors, portal blood inflow and intrahepatic vascular resistance, which are responsible for the hemodinamic changes in portal venous system.

The main complication of portal hypertension is esophageal and gastric varices development, and therefore the standard of care should be focused primarly on prophylaxy and secondly, in advanced cases, on variceal bleeding treatment.

We describe here the physiopathology of portal hypertension in cirrhosis, as well as the current management of the most important and potentially catastrophic complication, acute variceal bleeding.

Keywords: *liver cirrhosis, portal hypertension, esophageal variceal bleeding*

Rezumat

Hipertensiunea portală reprezintă o consecință majoră a cirozei hepatice, cu repercursiuni asupra calității vieții, ca hemoragia digestivă superioară prin efracția varicelor esofagiene. Fiziopatologia hipertensiunii portale din bolile cronice hepatice este dominată de doi factori: fluxul sanguin portal şi rezistența vasculară intrahepatică, care este responsabilă de tulburările hemodinamice din sistemul venos portal.

Complicațiile hipertensiunii portale sunt datorate dezvoltării varicelor gastrice şi esofagiene şi astfel, măsurile terapeutice standard sunt adresate profilaxiei primare şi secundare, in cazurile avansate şi pe tratamentul sângerării variceale.

Descriem astfel fiziopatologia hipertensiunii portale in ciroza hepatică şi tratamentul hemoragiilor majore variceale.

Cuvinte-cheie: *ciroză hepatică, hipertensiune portală, hemoragie variceală esofagiană*

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Introduction

Chronic liver diseases, particularly liver cirhossis are progressive conditions, that may present either in a compensated form in early stages, or in advanced cases, as the disease evolves, with certain manifestation of portal and parenchymatous decompensation. Portal hypertension develops when liver cirrhosis progresses, and is associated with several complications, including bleeding from esophageal varices or in portal decompensation with ascites, complications like spontaneous bacterial peritonitis or hepatorenal syndrome (1). So, the management of a patient with liver cirrhosis and portal hypertension depends on the „grade" of portal hypertension, appreciated by the presence or absence of esophageal varices, or in severe forms by acute variceal hemorrhage, when the primary goal is to control the bleeding and then to prevent the possible rebleeding episodes.

Physiopathology of portal hypertension

Portal hypertension is a hemodymanic abnormality that reffers to a pathological increase in hepatic venous pressure gradient beyond 5 mmHg, with clinical significance at values exceeding 10 mmHg. According to Ohm law applicated for fluids, portal pressure represents the product between the portal flow and the resistance to this flow, $\boldsymbol{P = Q \times R}$**.** Therefore, in cirrhosis, portal pressure increases on one hand due to the increase of portal inflow and on the other hand due to the increase of the resistance to portal flow, both intrahepatic and collateral (2). In addition, it is well known the role of the vasoactive factors (3), vasoconstrictor and vasodilatator substances that actively modulates the portal pressure, the active intrahepatic vasoconstriction accounting for 20-30% of the increased intrahepatic vascular resistance (2).

Hemodinamic background

In clinical practice, portal venous pressure is expressed as a gradient, hepatic venous pressure gradient (HVPG) (4), which represents the difference between the wedged hepatic venous pressure (WHVP) that reflects in fact the sinusoidal pressure and the free hepatic venous pressure (FHVP) which is equivalent to systemic venous pressure. Invasive measurement of portal pressure through portal vein catheterization is not routinely used. As we mentioned before, the preffered method for assessing the portal pressure is to determine HVPG, placing a catheter in a hepatic vein via femural or jugular route. First step, the catheter is wedged into one branch of the hepatic vein for measuring the WHVP (normal values between 6-10 mmHg). It was demonstrated that, in liver cirrhosis, WHPG correlates closely with portal pressure (5). Second step consists in removing the tip of the catheter for assessing the FVHP (3-6 mmHg). This correction is neccesary for cases with increases in intraabdominal pressure (2), like cirrhotic ascites.Therefore, by substracting the FHVP from WHVP results the HVPG, with normal values between 3 and 5 mmHg. Indirect assessment of portal pressure measuring HVPG represents the actual standard for diagnosing and monitoring of the portal pressure after pharmacological therapy and after certain therapeutical procedures for decreasing the

portal pressure (6). Changes in HVPG have predictive value for the development of portal hypertension complications, especially variceal bleeding (7). So, portal hypertension is considered clinically significant with esophageal varices development when HVPG exceeds 10 mmHg, while the risk of variceal hemorrhage increases when HVPG is higher then 12 mmHg (8).

Vascular resistance

One of the most important determinants of portal hypertension in end-stage liver disease is represented by increased resistance to portal blood flow (9) due to structural abnormalities that characterize liver cirrhosis: fibrosis, regenerative nodules, hepatic arhitectural distorsion. According to Poiseuille law applied to portal circulation, portal vascular resistance is indirectly proportional to the fourth power of the vessel radius. Changes of the vessel diameter can modify the portal resistance. Therefore, the decrease of the vessel radius will determine the increase of the portal vascular resistance, and subsequently of the portal pressure. In liver cirrhosis, vascular changes occur in hepatic microcirculation, and are responsible for the increase in hepatic vascular resistance and for producing the sinusoidal portal hypertension. Perisinusoidal collagen deposition, sinusoid capillarization can contribute to portal hypertension development. In addition, endogenous factors with contractile properties, like myofibroblasts and activated stelatte cells, augment the vascular resistance, acting as a dynamic component.

Portal inflow

The second factor involved in the pathogenesis of portal hypertension is the increase of the portal blood flow, which develops secondary to the splanchnic arteriolar vasodilatation and and to other systemic changes that characterise the hyperdynamic circulation typical for liver cirrhosis. It is generally accepted that splanchnic arteriolar vasodilatation is a multifactorial phenomenon and implies several mechanisms, both local and also neurogenic and umoral factors (10). The augmentation of portal venous inflow in liver cirrhosis on one hand, aggravates the portal hypertension, and on the other hand explains the maintaining of an increased portal pressure despite the developing of portosystemic collaterals that can divert as much as 80% of portal inflow. Splanhnic vasodilatation and more than that, systemic vasodilatation are the main elements of the hyperdynamic state in liver cirrhosis. Variate endogenous vasodilatator substances (nitric oxide, prostacyclin, endotoxins) are responsible for inducing the specific manifestations like arterial hypotension, hypervolemia, increased cardiac output and decrease of peripheral resistance. Vasodilatator changes are also encountered in pulmonary and gastric circulation and play an important role in hepatopulmonary syndrome and portal gastropahy development (11). Portal hypertension is associated with an expansion of the plasmatic volume, reversible to a low-sodium diet and diuretic therapy (9). Studies from literature state for a relationship between arterial hypotension, the severity of liver failure and the survival rate, suggesting a possible connection between the grade of hyperdynamic circulation and long-term prognosis in liver cirrhosis (12).

Vasoactive factors

It is now well recognized the role of the vasoactive substances, both vasodilatators and vasoconstrictors in the physiopathology of portal hypertension, in splanhnic vasodilatation development and also in increasing the hepatic and collateral vascular resistance. In liver cirrhosis, high plasmatic concentrations of vasoconstrictors like adrenalin, endothelin, angiotensin II are found and also it has been demonstrated an exaggerated vascular response to these factors, explaining their role in increasing the portal pressure (13). Endothelin 1 is considered the most powerful vasoconstrictor and in addition it has fibrinogenetic properties, influencing both the dynamic and the passive component of the hepatic resistance (14). Angiotensin II also plays an important part in vascular resistance modulation, on one hand due to renin-angiotensin-aldosterone system and on the other hand due to angiotensin II type I receptors, expressed by the stellate cells, leading to contraction and proliferation (15, 16). Therefore, the stellate cells that surround hepatic sinusoids have an active role in increasing the hepatic resistance through a dynamic component. In addition, it has been stressed that the adrenergic neurohumoral system influences this vasoconstrictor response, owing to adrenalin production by stellate cells, with autocrin self-stimulation (17). More than that, it is well known that cirrhotic patients express an increased sympathomimetic tonus. The vasoconstrictor response is counterbalanced by a vasodilatator reaction, ascribed especially to nitric oxide, which is the most well known endogenous vasodilatator substance. It is synthetised in a multitude of tissues from L-arginine, as a result of NO-synthetase action. In liver cirrhosis, intrahepatic production of vasodilatators is reduced due to endothelial cells dysfunction and probably due to an increased hepatic degradation (18). Relative deficiency of NO in liver cirrhosis lead to increase the vascular resistance to portal blood flow, and subsequently to increase the portal pressure. The role of NO in regulating hepatic microcirculation and also splanhnic circulation is now well defined. Vasodilatator mediators are responsible for the hyperdynamic state that characterize liver cirrhosis, through an overproduction, either through a diminished hepatic metabolism, either through liver shunting via collaterals. In addition, there has been noticed a decrease response to vasoconstrictor substances (19). Other studies emphasized the role of intestinal peptides like glucagon, vasoactive intestinal peptide, bile salts, substance P, calcitonin gene-related peptide in splanhnic arteriolar vasodilation, owing to elevated plasmatic levels through portosystemic shunting. Increased levels of plasmatic glucagon are responsible for 30-40% of the splanchnic vasodilation in patients with portal hypertension, suggesting the pathogenic role of glucagon and supporting the use of glucagon antagonist, somatostatin, in the management of variceal bleeding (20).

Esophageal varices and variceal bleeding

Esophageal varices development represents a major consequence of portal hypertension in liver cirrhosis and is associated with important morbidity and mortality in case of bleeding. HVPG plays a determinant role in varices formation, when exceeds 10 mmHg, with increasing risk of bleeding at values greater than 12 mmHg (21). Esophageal varices are portosystemic collaterals located at the gastroesophageal junction, and

decompress the portal system, diverting the portal blood flow in general circulation *(Figure no.1).*

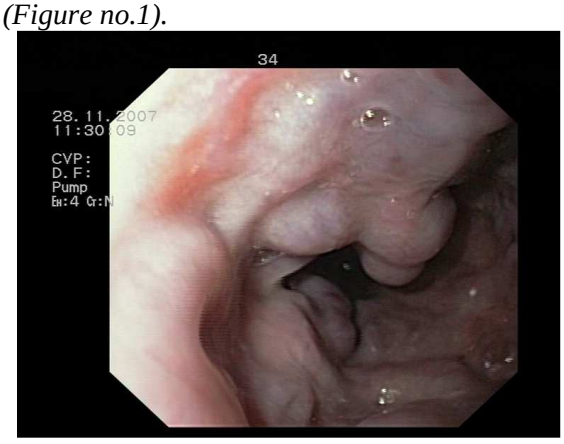

Figure no.1: *Esophageal varices grade III. Endoscopic aspect.*

Data from literature outlines that the majority of patients with liver cirrhosis develop esophageal varices and their natural course consists in growing and bleeding (22). The rate of development of new varices ranges between 5-12% per year, while the rate of size increasing varies between 6 and 70% every two years (22). Prevalence of esophageal varices among cirrhotic patients is variable, depending on the severity of liver dysfunction. Approximately 30% of patients with liver cirrhosis present with esophageal varices in compensated stage and 60% when the disease become decompensated (23).

Upper digestive endoscopy is the gold standard for diagnosis the presence of varices and all the new patients with liver cirrhosis should be screened to detect esophageal varices (24). Although several noninvasive predictors of the presence of varices have been imagined, like the ratio between platelet count and spleen diameter, no method has been validated for routine use (25). Regarding endoscopic surveillance of esophageal varices, upper digestive endoscopy should be performed every 3 years in cases without varices at first examination; in patients with small varices, the surveillance interval should be 1-2 years, choosing the shorter interval for patients with alcoholic cirrhosis, severe liver dysfunction, endoscopic risk signs for bleeding and faster varices growth (24). Large varices do not need endoscopic surveillance, but prevention of the first bleeding episode should be performed.

Variceal bleeding, the most threatening complication of portal hypertension and liver cirrhosis carries out a poor prognosis and a high mortality rate of 20% at 6 weeks, although several progresses in management of active hemorrhage have been made (26).There have been identified certain predictors for the risk of variceal bleeding: variceal size, severity of liver dysfunction expressed by Child-Pugh score, HVPG greater than 12 mmHg, presence of endoscopic risk signs (27). Among these, variceal size seems to be the most important predictor for the first hemorrhage, as the high risk for bleeding appears in patients with large varices (2). The mechanism of variceal rupture is related to the tension in the varices wall, which is influenced on one hand by vessel diameter and on the other hand by the pressure within the varix, expressed by HVPG. This theory derives from Laplace law, which considers that wall tension is directly proportional with vessel diameter and also with transmural pressure and indirectly proportional with variceal wall thickness. There were documented several risk factors for recurrent variceal bleeding, such as the severity of initial bleeding, aggressive resuscitation with plasma-expanders,

clinically apparent, as well as inapparent infections, HVPG, complications of endoscopic treatment, renal failure (28).

Management of variceal bleeding

Primary prophylaxis

According to physiopathological mechanisms mentioned earlier, the therapeutical goal for preventing variceal bleeding is to reduce HVPG below 12 mmHg (8,9). In addition, it has been stated that the risk of recurrent bleeding is reduced when HVPG decreases with more 20% from baseline (30). The management of first bleeding episode is conducted according to variceal size. Therefore, in patients with small varices, pharmacological treatment is the option of choice.Non-selective beta-blockers should be used to prevent variceal growth and in those cases associated either with advanced liver disease, either with endoscopic risk signs for bleeding in order to prevent variceal rupture (31). Non-selective beta-blockers decrease the portal pressure through two effects: reduce the cardiac output, which is a beta-1 effect and a beta-2 effect represented by splanchnic vasoconstriction, with secondary decreasing the portal flow (2). Current medication includes propranolol, nadolol or carvedilol for preventing the first variceal hemorrhage. Carvedilol seems to be more effective in reducing the portal pressure comparing to propranolol, although no studies assess the efficacy of carvedilol in primary prophylaxis (32). Isosorbide mononitrate showed no effect in prophylaxis of first bleeding episode and should not be used in patients with liver cirrhosis and portal hypertension, either alone or in combination with beta-blockers (31). The second therapeutical option is reserved to patients with medium or large esophageal varices and consists in prophylactic endoscopic band ligation (31). EBL is more effective than beta-blockers in preventing first variceal hemorrhage, without improving survival rate (31). The study of Tripathi, who compared carvedilol with EBL in preventing the first variceal bleed, outlined an interesting result, that is a lower rate of bleeding with the use of carvedilol, with no differences on long-term survival (32). This is the first trial which demonstrates an advantage of drug therapy over variceal ligation in preventing variceal hemorrhage. But, there is a limitation of this study, related to the measurement of HVPG, which was not performed as an assessment of reducing the portal pressure. Therefore it is imposible to determine if the lower rate of bleeding in case of carvedilol was due to failure of EBL or due to a real benefit of decreasing the portal pressure.

Treatment of acute variceal hemorrhage

Acute variceal bleeding is the most life-threatening complication of portal hypertension, with a significant mortality, which ranges between 5 to 50% in cirrhotic patients (33). Although recently has been reported an improvement in the mortality associated with acute hemorrhage due to endoscopic approach, the long-term survival is still poor, owing to early rebleeding, development of liver failure or other complications of the liver disease. Management of acute variceal bleeding includes on one hand general measures and on the other hand, specific measures to control the hemorrhage *(Figure no 2, see next page).*

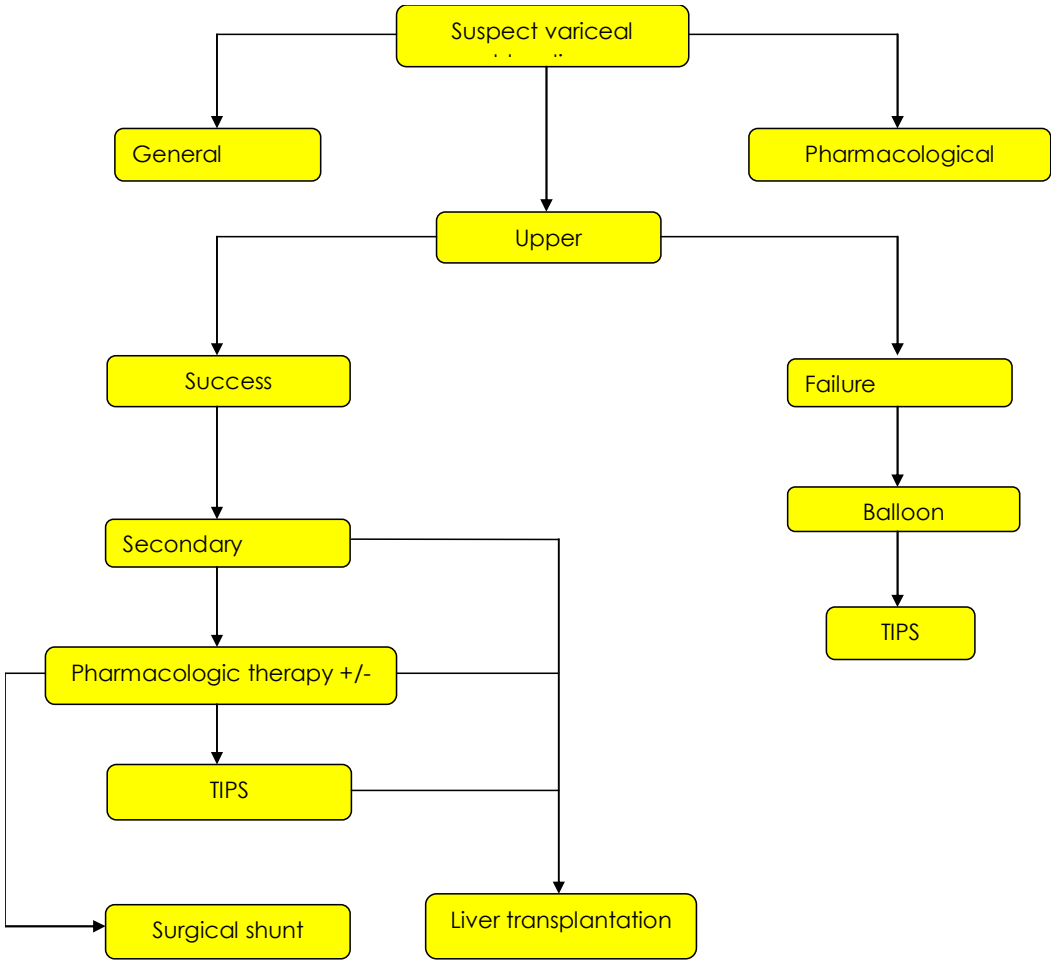

Figure no.2: *Algorithm of treatment of acute variceal bleeding*

General measures refer to initial resuscitation, which is indicated in case of hemodynamic unstable patients. Hypovolemia should be corrected using saline solutions and blood replacement to maintain hemoglobin around 9-10g/dl. Overtransfusions should be avoided because may increase the portal pressure, precipitate a rebleeding episode and worsen ascites accumulation. Fresh frozen plasma and platelet transfusions are indicated in case of coagulopathy or severe thrombocytopenia, when platelet count is below $50x10^9$/L. Cirrhotic patients with upper digestive hemorrhage present a significant risk for developing bacterial infections due to endotoxinemia, either spontaneous bacterial peritonis or other infections and are associated with failure to control bleeding or early rebleeding (34). For this reason, a short-term prophylaxis with antibiotics should be used in order to prevent early variceal rebleeding (34). Specific measures to control acute variceal hemorrhage consist of pharmacologic and endoscopic therapy. Pharmacologic

therapy is initiated when the variceal source of bleeding is suspected, even before performing upper endoscopy. Vasopresin is considered the most potent splanchnic vasoconstrictor which decreases the portal inflow and subsequently the portal pressure, but which also has multiple side effects that limit its clinical use. The standard dose is 0,2-0,4 units/minute at continous intravenous infusion and can be increased to 0,8 units/minute for maximum 24 hours, always with concomitent administration of iv nitroglycerin to diminish the cardiac side effects (2). The most routinely used medications are terlipressin, a synthetic analogue of vasopressin and octreotide, a somatostatin analogue. Terlipressin acetat or glypressin is efficient in controlling acute variceal bleeding, has fewer side effects comparing to vasopressin and is associated with a decreased mortality rate (35).The initial dose is 2 mg iv every 4 hours, with reducing the dose at 1 mg every 4 hours, once the hemorrhage is controlled. Octreotide has the same effect on splanchnic circulation due to inhibition of vasodilatatory peptides, such as glucagon, leading to portal pressure decreasing. Sandostatin, the trade name, is a safe medication, used at an initial bolus of 50 µg followed by 50 µg /hour in continuous infusion for a 5 days period. Upper digestive endoscopy should be made as soon as possible, within 12 from admission, especially in cirrhotic patients with significant bleeding, in order to detect esophageal varices and to perform endoscopic therapy (31).

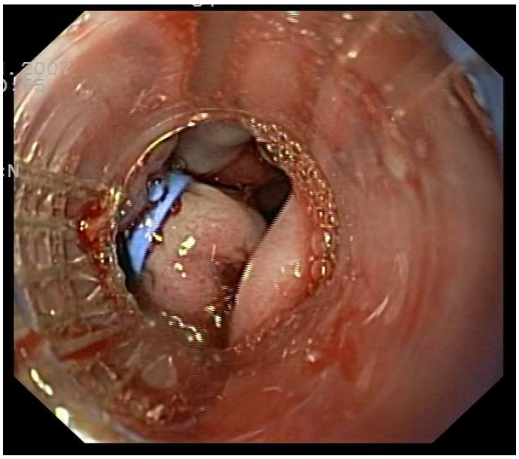

Figure no.3: *Variceal banding in acute hemorrhage*

The best endoscopic treatment, established by consensus, is considered esophageal variceal ligation *(Figure 3)*, with clear benefits upon sclerotherapy in the initial control of variceal bleeding (31). Sclerotherapy should be performed only if ligation is not technically possible (31). Balloon tamponade is indicated in massive bleeding, for maximum 24 hours, as a temporary bridge to a definitive therapy. If emergency endoscopic treatment and pharmacological therapy fail to control bleeding, which is happening in 10-20% patients (2), other therapies for portal decompression should be considered.

In Child A cirrhosis, a shunt procedure is preffered, while in cases with severe liver dysfunction and decompensated cirrhosis, TIPS is the best therapeutic option (36). Some authors report hemorrhage control if a portocaval shunt is performed with 8 hours from onset of bleeding (37), but this approach is not routinely used in practice. TIPS is indicated in refractory acutely bleeding varices *(Figure no.4 a,b,c from the next page)*, despite aggressive management, but not in patients who have bled only once from esophageal varices (38). Transjugular intrahepatic portosystemic shunt procedure consists in performing an intrahepatic channel between right hepatic vein and portal vein, using a

metallic self-expandable stent with the aim of diverting the blood flow into systemic circulation.

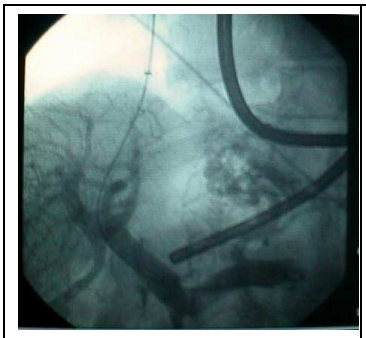

Figure no.4a: *Intrahepatic portocaval shunt; Angiographic aspect*

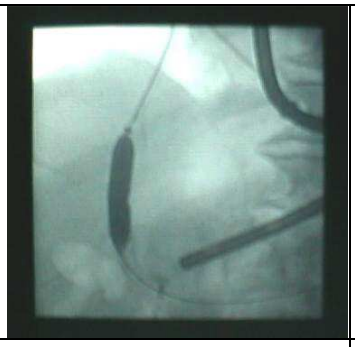

Figure no.4b: *TIPS: technical procedure*

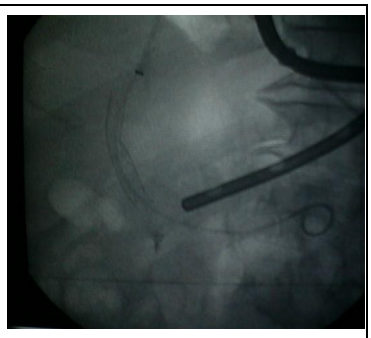

Figure no 4c: *TIPS*

Secondary prophylaxis

Prevention of rebleeding should start from the 6-th day of the first episode of variceal hemorrhage (31). Early rebleeding is a well documented phenomenon and it occurs in 50% of patients in the first 6 weeks after the first bleeding episode, with an increased risk in cases with sever liver impairment (33). There have been proposed several therapeutical modalities, depending on previous use of prophylactic treatment. Endoscopic band ligation is the endoscopic method of choice for preventing rebleeding, because it proved to be superior to sclerotherapy (39). The combination of beta-blockers and band ligation is now considered the best therapeutical option in case of cirrhotic patients who did not receive primary prophylaxis and bled (31). In case of patients who already have received primary prophylaxis with beta-blockers and present with variceal hemorrhage, the attitude consists is adding band ligation, every two weeks, until eradication of varices is obtained. In case of patients with contraindications or intolerance to beta-blockers, esophageal band ligation is the preffered method for preventing rebleeding (31). The category of patients who fail to respond to pharmacological combined with endoscopic treatment, should be reffered for portal decompressive operations or TIPS, depending on cirrhosis severity (31). There are several types of shunt procedures: nonselective total portosystemic shunts, non-selective partial portosystemic shunts and, the most used selective, respectively splenorenal shunts (36). Despite the benefit of achieving hemostasis, there is no improvement in survival rate, compared to endoscopic techniques (36). Liver transplantation remains a salvage therapy for patients in Child B/C cirrhosis, providing good long-term outcomes, while TIPS may be used as a bridge to transplantation (31).

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