Pharmacological Therapy of Portal Hypertension

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Abstract: Portal hypertension is a clinical syndrome characterized by pathological elevation of portal venous pressure and all its consequences. In portal hypertension, there is an increase in pressure in the veins that carry blood from the splanchnic organs to the liver. The main factors of portal hypertension include increased intrahepatic resistance to portal blood flow due to degenerative nodules and increased splanchnic blood flow secondary to vasodilation in the splanchnic vascular bed. Clinical symptoms indicated in portal hypertension are varicella hemorrhage with hematemesis or vomiting of blood (vomitus may be red blood mixed with clumps or coffee grounds), and/or melena, i.e. red or black defecation-like petis (shrimp paste). The goal of treatment of patients with portal hypertension is to reduce portal pressure. Drugs for portal hypertension should be able to lower blood vessel portal pressure without lowering arterial pressure, which may aggravate hyperdynamic circulation and increase the risk of renal failure. Most of the drugs often used in clinical practice are splanchnic vascular vasoconstrictors vasopressin derivatives (terlipressin), somatostatin, somatostatin analogs (octreotide and vapreotide), Nonselective β-Blocker and Carvedilol.

1 INTRODUCTION

Portal systems are all venous systems that drain blood from the gastrointestinal tract from the abdominal cavity, spleen, and gallbladder to the liver. The portal vein is the unification of the superior mesenteric veins and the cervix. The height of the portal pressure is determined by the interaction between portal flow and the vascular pressure that blocks it (Minano and Garcia-Tsao, 2010; Waspodo, 2012).

Portal hypertension is a clinical syndrome characterized by pathologic elevation of portal venous pressure and all its consequences. In portal hypertension, the Hepatic venous pressure gradient (HVPG) rises above the normal value of 5 mm Hg. A further increase above 10 mmHg is called clinically significant portal hypertension (CSPH). The most common initial consequences of portal hypertension are the formation of varicose veins in the stomach and esophagus that can rupture and cause bleeding (El-Tawil, 2012).

The goal of therapy in patients with portal hypertension is to reduce portal pressure. Drugs used are expected to reduce portal pressure without decreasing mean arterial pressure (MAP) and increasing the risk of renal failure. Ideal pharmacological therapy is also expected to maintain or even improve liver perfusion that can improve liver function (Berzigotti, 2014). This review discusses portal hypertension therapy especialy in pharmacological management.

2 PATHOPHYSIOLOGY

In portal hypertension, there is an increase in pressure on the veins that carry blood from the splanchnic organs to the liver. According to Ohm's Law ($\Delta P = F \times R$), pressure (P) will increase if there is an increase in the amount of flow (F) and/or increase in resistance to flow (R). So anything that causes increased portal blood flow or resistance/portal blood vessel resistance can lead to portal hypertension (Seo, 2011).

There are two main factors of portal hypertension: 1) Increased intrahepatic resistance to portal blood flow due to degenerative nodules and 2)

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Increased splanchnic blood flow secondary to vasodilation in the splanchnic vascular bed (Nurdjanah, 2014; Garcia-Pagan et al., 2012).

2.1 Intrahepatic Circulation

Intrahepatic blood vessel resistance is caused by massive structural damage due to fibrosis/cirrhosis and intrahepatic vascular vasoconstriction. This is the primary cause of portal hypertension in cirrhosis (Iwakiri, 2014). Causal factors include:

2.1.1 Endothelial cell dysfunction

Liver endothelial cells (LSECs) are the first line of liver defense to injury and have various effects on liver function including blood clearance, liver cirrhosis and portal hypertension (Thabut and Shah, 2010; Iwakiri, 2014), blood vessels, hepatocyte growth immunity and angiogenesis/sinusoidal remodeling. Therefore, endothelial cell dysfunction can cause vasomotor control disorders (especially vasoconstriction), inflammation, fibrosis, and liver regeneration disorders that all facilitate the occurrence.

2.1.2 Reduced vasodilator

Nitric oxide (NO) is the most potent vasodilator molecule known today. In liver cirrhosis, NO production/bioavailability is significantly reduced resulting in increased intrahepatic blood vessel resistance.

There are at least two mechanisms that explain the decrease in NO production. First, the NO forming enzyme (endothelial NO synthase / eNOS) is inhibited by negative regulators (such as Caveolin-1) that increase during cirrhosis so NO production decreases.

Second, oxidative stress increases in cirrhosis. Increased superoxide radicals react with NO to form peroxynitrite (ONOO-), an endogenous toxin thus reducing the bioavailability of NO as a vasodilator. Antioxidant molecules such as vitamin C, vitamin E, superoxide dismutase, and N-acetylcysteine have been shown to improve intra-hepatic blood vessel resistance and portal hypertension (Garcia-Pagan et al., 2012; Iwakiri, 2014).

2.1.3 Increased vasoconstrictors

In cirrhosis, other than decreased vasodilators, there are also increased vasoconstrictors such as thromboxane A2 (TXA2). TXA2 is produced by the role of cyclooxygenase-1 (COX-1) in LSECs. Increased COX-1 activity in liver cirrhosis results in a larger amount of TXA2 and increases intrahepatic blood vessel resistance. Endothelin (ET-1) is another important vasoconstrictor in this mechanism when it binds to the Hepatic Stellate Cells (HSCs) receptor (Iwakiri, 2014; Garcia-Pagan et al., 2012).

2.1.4 Stellate cell activation

HSCs are located in the space between LSECs and hepatocytes. In liver injury, HSCs are activated and converted into myofibroblasts, which initiate proinflammatory and fibrotic expressions. HSCs become contractile at this active stage. Increased active HSCs around the newly formed sinusoidal blood vessels increase intrahepatic blood vessel resistance in cirrhosis. Active HSCs have a decreased response to vasodilators including NO. In addition, ET-1, which increases in cirrhosis, increases contraction of HSCs. Increased ET-1 production and reduced NO production in cirrhosis increase intrahepatic resistance to portal blood flow. However, manipulation with ET receptor antagonists is complex because vasoactive effects vary with cellular location (Iwakiri, 2014).

2.1.5 Angiogenesis in the liver

In portal hypertension, angiogenesis plays an important role in intrahepatic circulation. In liver cirrhosis, there is an increase in the number of septa fibrosis and adjacent regenerative nodules. Active HSCs and/or other myofibroblasts, such as portal myofibroblasts, allegedly cause angiogenesis in liver cirrhosis. HSCs actively activate LSECs by releasing angiogenic factors, such as angiopoietin and vascular endothelial growth factor (VEGF). The irregular flow patterns generated as a result of the separation (or intussusception) angiogenesis may contribute to the increase in intrahepatic blood vessel resistance (Seo, 2011; Iwakiri, 2014).

2.2 Extrahepatic Circulation

After the occurrence of portal hypertension, it soon forms a collateral portosystemic blood vessel. The blood from the digestive organs shifts to the collateral vessels, but the portal blood flow flowing from the splanchnic circulation increases to compensate this. Increased portal blood flow aggravates portal hypertension.

Furthermore, arterial vasodilation in the splanchnic and systemic circulation obtained in

cirrhosis helps to increase blood flow to the portal vein (Iwakiri, 2014).

Portosystemic collateral blood vessels arise in response to increased portal pressure. Collateral vessels are formed from the opening of blood vessels that existed before or developed through angiogenesis.

The presence of collateral blood vessels can lead to serious complications, including variceal hemorrhage and hepatic hepatopathy. Changes in portal pressure are alleged to be the first to be detected by vascular beds in the intestine, followed by arteries in the splanchnic circulation. This vascular bed then produces various angiogenic factors such as VEGF and placental growth factor (PlGF) that trigger the formation of a portosystemic collateral (Iwakiri, 2014; Seo, 2011).

Arterial vasodilation in the splanchnic and systemic circulation of NO is the major vasodilator molecule that causes excessive vasodilatation of the splanchnic and systemic circulatory arteries in excessive portal hypertension. Experimental studies of portal hypertension, with or without cirrhosis, have shown that other vasodilator molecules, such as carbon monoxide (CO), prostacyclin, endocannabinoid, and endothelium-derived hyperpolarizing factor (EDHF) are also involved. Increased portal pressure triggers eNOS activation and follows increased NO production. At first, a small increase in port pressure will affect the intestinal microcirculation and then increased VEGF production followed by increased eNOS. As porta pressure continues to rise to some degree, vasodilation develops in the splanchnic circulatory artery (e.g. the mesenteric artery). Vasodilation then arises also in the systemic circulatory arteries (e.g. aorta). This process leads to hyperdynamic circulation characterized by peripheral and splanchnic vasodilation, reduced MAP and increased cardiac output (Iwakiri, 2014; Seo, 2011).

2.3 Clinical Symptoms

Increased pressure in the portal vein can cause esophageal or gastric varices. Bleeding from these varicose veins is usually severe and in the absence of immediate treatment can be fatal.

The symptoms of variceal bleeding may be hematemesis or vomiting of blood (vomitus may be red blood mixed with clumps or coffee grounds), and or melena, i.e., red or black defecation like petis (shrimp paste).

Once the varicose veins bleed, they tend to bleed again and the likelihood of dying from each episode of bleeding is quite high (30% -35%). Other consequences of portal hypertension may be ascites, spontaneous bacterial peritonitis, hepatorenal syndrome, hepatopulmonary syndrome and hepatic hepatopathy (Garcia-Pagan et al., 2012; Kusumobroto, 2015).

2.4 Diagnosis

Diagnosis of Portal hypertension is made on the basis of anamnesis and physical examination of clinical symptoms and investigations. Portal pressure > 10 mmHg with invasive examination and measurement of the hepatic venous pressure gradient (HVPG) through hepatic venous catheterization gives equivalent results to portal pressure/portal pressure (PP) (Bosch, 2008; Cahyono, 2014).

The measurement of portal pressure in patients with portal hypertension is important in evaluating the effectiveness of different therapies. The most commonly used method is catheterization of the hepatic vein with a balloon catheter to determine HVPG which is the difference in pressure of the hepatic vein that is wedged or clogged with free hepatic venous pressure. Although the HVPG measurement procedure is relatively simple and safe, it is not widespread because it is invasive and there is not enough standardization (Minano and Garcia-Tsao, 2010).

In portal hypertension, an increase in portosystemic pressure can occur in any part of the portal vein system. The various possible etiologies according to location are listed in Table 1. Although portal hypertension may be a result of prehepatic, posthepatic and intrahepatic non-cirrhosis abnormalities, cirrhosis is the most frequent cause of portal hypertension (Bari, 2012). Liver cirrhosis causes 90% of cases of portal hypertension in Western countries. When cirrhosis is first diagnosed, varicose veins have been present in 30-40% of patients with compensated cirrhosis and 60% in decompensated cirrhosis patients (Bosch, 2008).

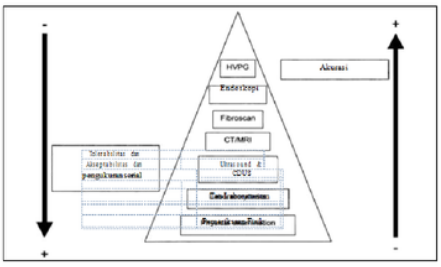

Figure 1: Diagnosis of Portal Hypertension (Bosch, 2008)

Table 1: Etiology of Portal Hypertension by Location of Increased Portal Blood Resistance (Waspodo, 2012; Bosch, 2008).

PREHEPATIC- Splanchnic Venous Thrombosis
- Pressure/external compression of portal vein
- Portal Vein Thrombosis
- Congenital Portal Vein Stenosis
- Arteriovenous Fistula
INTRAHEPATIC Presinusoidal- *Non Cirrhotic Intrahepatic Portal Hypertension (NCPH)*
- Primary Biliary Cholangitis
- Primary Sclerosing Cholangitis-Cirrhosis
- Vitamin A intoxication
- Infiltrative Disorders (lymphoproliferative or mieloproliferative) Postsinusoidal-Vena-okskusif Disease
POSTHEPATIC
- Hepatic Vein Thrombosis
-Congenital Malformations and Inferior Vena Cava Thrombosis-Budd-Chiari Syndrome
- Invasion of Vascular Tumor
- Constrictive Pericarditis

2.5 Portal Hypertension Therapy

The goal of treatment in patients with portal hypertension is to reduce portal pressure. In subclinical portal hypertension therapy aimed to avoid Clinically Significant Portal Hypertension (CSPH), asymptomatic patients with CSPH should be treated to lower the portal blood vessel pressure below 10 mmHg as well as CSPH that is known to increase the risk of decompensation (Berzigotti, 2014).

Portal hypertension therapy and the treatment of the major complications of variceal hemorrhage include pharmacological and nonpharmacological therapy.

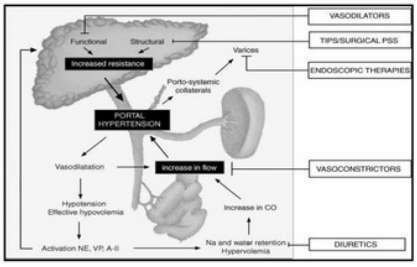

Figure 2. Basic Rational Therapy for Portal Hypertension (Bosch *et al*., 2008)

Nonpharmacological therapy includes endoscopic band ligation, sclerotherapy, varicose embolization with N-butyl-2-cyanoacrylate, tamponade and a transjugular intrahepatic portosystemic shunt (TIPS). In this literature review, the discussion emphasizes pharmacological therapy of portal hypertension.

3 PHARMACOLOGICAL THERAPY OF PORTAL HYPERTENSION

Varicose veins and variceal hemorrhage in adult patients with cirrhosis need to be grouped according to the clinical disease stage that differs from portal hypertension:

1. Patients with cirrhosis and portal hypertension that have not yet had varicose veins: the goal of therapy is to prevent the formation of varicose veins (Pre-primary prophylaxis).
2. Patients with gastro-esophageal varicose veins who have never experienced bleeding: the goal of therapy is to prevent variceal bleeding (Primary prophylaxis).
3. Patients with acute varicella hemorrhage: the goal of therapy is to stop the bleeding and prevent recurrence of early bleeding.
4. Patients who have experienced and survived acute varicella veins: the goal of therapy is to prevent recurrence of advanced bleeding (Secondary Prophylaxis) (Bari, 2012; Garcia-Tsao, 2016).

3.1 Frequently Used Drug Groups in Clinical Practice

Most of the drugs used in clinical practice are splanchnic vascular vasoconstrictors, which work by decreasing splanchnic blood flow and hyperkinetic circulation (Berzigotti, 2014).

3.1.1 Vasopressin derivative of Terlipressin

Vasopressin derivative of Terlipressin (triglycyl lysine vasopressin) is a long-acting synthetic vasopressin analog with longer biological activity and a better safety profile. Terlipressin has an affinity for vascular receptors higher than vasopressin. It has a splanchnic circulatory vasoconstriction effect, increases arterial blood pressure and systemic vascular resistance, and decreases cardiac output. This drug is given intravenously by injection 2 mg/4 hours for 24-48

hours, followed by 1 mg/4 hours for 2-5 days. Until now Terlipressin has not been approved for use in the United States (Minano and Garcia-Tsao, 2010; Berzigotti, 2014).

3.1.2 Somatostatin

Somastotatin is a peptide with 14 amino acids secreted by nerve cells, endocrine, and enteroendocrine cells in the hypothalamus and digestive system (stomach, intestine, and pancreatic delta cells). Somatostatin induces splanchnic vasoconstriction thereby reducing port pressure. Somatostatin has a very short half-life when given by intravenous infusion at 250-500 mg/h, after a bolus of 250 mg, for 5 days (Berzigotti, 2014; Garbuzenko, 2015).

3.1.3 Somatostatin Analog

In order to overcome the major limitation of somatostatin's short half-life, long-acting analogs of somatostatin have been developed, including Octreotide, Vapreotide, Lanreotide, and Seglitide. Octreotide and Vapreotide have a longer half-life than somatostatin but have short-term effects on portal vascular pressure due to rapid desensitization. The drug is administered by intravenous infusion of 50 µg / h, after a 50 µg (optional) intravenous or subcutaneous bolus, for 5 days (Minano and Garcia-Tsao, 2010).

Nonselective β-Blocker (NSBB), singly or in combination with NSBB vasodilator lowers portal pressure by reducing portal-collateral blood flow. NSBB blocks both the β-1 receptors in the heart thus reducing cardiac output, as well as β-2 receptors in the blood vessels so that no α-1 adrenergic blockage activity causes splanchnic vasoconstriction. Other beneficial effects are reduced blood flow to azygos vein and thus varicose pressure, as well as shortening the intestinal transit time associated with a decrease in bacterial overgrowth which reduces the risk of bacterial translocation. NSBB is a cheap, safe, and easy-to-use drug, reducing the risk of all major complications associated with portal hypertension and increases survival rates (Berzigotti, 2014; Garbuzenko, 2015).

Propranolol is a β-1 and β-2 adrenergic receptor antagonist. This drug induces decreased cardiac output and splanchnic vasoconstriction. The drug is administered orally, starting with 1-20 mg twice daily, with increasing dosage every 2-3 days to the maximum tolerable dose (making arterial systolic pressure > 100 mmHg and heart rate > 50 times per minute). Dosage should be no more than 320 mg/day and should be evaluated for its long-term effects. The success of therapy in cirrhosis can be assessed when HVPG is reduced to < 12 mmHg or ≥20% of its pre-therapy value (Berzigotti, 2014).

Nadolol is a β-1 and β-2 adrenergic receptor antagonist. This drug induces decreased cardiac output and splanchnic vasoconstriction. The drug is administered orally, once daily starting at a dose of 20 mg, increasing every 2-3 days to the maximum tolerable dose (making arterial systolic pressure > 100 mmHg and heart rate > 50 times per minute). The dosage should not exceed 160 mg/day and should be evaluated for its long-term effects. The success of therapy in cirrhosis can be assessed when HVPG is reduced to < 12 mmHg or ≥20% of its pre-therapy value (Berzigotti, 2014).

The effects of NSBB on portal pressure can be increased when combined with drugs that increase liver vascular tone. This has been tested by combining isosorbide mononitrate (ISMN) with propranolol or nadolol. ISMN is an exogenous NO donor that is absorbed through oral administration. ISMN reduces port pressure without reducing blood flow to the liver. Its mechanism of action is thought to decrease liver resistance through intrahepatic NO administration. Another drug that has been tested to enhance the effects of NSBB on portal pressure is prazosin, a α-adrenergic blocker. This combination not only lowers HVPG but also enhances liver perfusion (Berzigotti, 2014; Garbuzenko, 2015).

Carvedilol is also a β-1 and β-2 (NSBB) adrenergic receptor antagonist with intrinsic anti-α1 adrenergic activity, so, the effects of carvedilol are similar in combination with NSBB and prazosin. Carvedilol has a much greater effect in decreasing porta pressure (16%-43% than before therapy) than propranolol or nadolol (12%-13% compared to treatment). This drug induces decreased cardiac output, splanchnic vascular vasoconstriction, and intrahepatic vasodilation. Carvedilol is given twice daily.

3.2 Other Drugs that Reduce Port Stress but Are Rarely Used

There are human studies on the administration of Statin (3-Hydroxy-3-methylglutaryl coenzyme A reductase inhibitor) to reduce the pressure of intrahepatic vascular resistance and improvement of hepatic blood flow in the presence of vasodilation in liver cirrhosis.

This is mediated by increased NO production due to improved liver vascular endothelial tissue by increasing endothelial Nitric Oxide Synthase

(eNOS). Simvastatin 20-40 mg/day for 1 month is proven safe and significantly decreases porta pressure. The addition of simvastatin in patients who have received NSBB is also proven effective in protecting against complications associated with portal hypertension (Berzigotti, 2014).

Inhibitor of the Aldosterone Renin-Angiotensin System. The renin-angiotensin-aldosterone system (SRAA) has an important role in regard to hypertension. Two drugs that work on SRAA that are currently widely used include angiotensin-converting enzyme inhibitors (ACEI) and angiotensin receptor blockers (ARBs) to reduce port pressure in compensated cirrhosis patients (Child-Pugh score, A). The resulting decrease is smaller when compared to NSBB. However, in decompensated cirrhosis, the use of RAAS inhibitors is contraindicated because it can increase the risk of hypotension and renal failure (Berzigotti, 2014).

3.3 Other Drugs and Theraupetic Strategies in Research

a. The etiological therapies of cirrhosis (such as antiviral therapy in hepatitis C and hepatitis B, cessation of alcohol use in alcoholic cirrhosis, immunosuppressants in autoimmune liver disease, iron supplements in haemochromatosis, copper clarity in Wilson disease) can modify the disease course pathways by repairing fibrosis, and prevent or inhibit the occurrence of portal hypertension (Garbuzenko, 2015; Berzigotti, 2014).
b. Obesity is an independent risk factor for the development of decompensated cirrhosis. An increase in body mass index after 1 year of monitoring may be associated with increased portal pressure. This suggests that there is a relationship between obesity and portal hypertension with an unknown mechanism. Leptin is allegedly associated because it is up-regulated in obesity and cirrhosis, thus inducing a decrease in the availability of NO, vascular dysfunction and liver fibrosis. Therefore, weight reduction can be a nonpharmacological strategy to reduce portal vascular pressure in patients with excess weight cirrhosis (Berzigotti, 2014).
c. Recently research has aimed at finding drugs that affect the basic mechanisms of portal hypertension in liver cirrhosis, especially drugs that suppress liver fibrogenesis in the early stages. No antifibrotic drugs have been specifically proven in clinical use. Some compounds that have a mechanism of fibrogenesis are at the study stage. Some natural antifibrotics show antioxidant ability and are anti-angiogenetic (Berzigotti, 2014; Garbuzenko, 2015).
d. Oxidative Stress Reduction Drugs. Similar to other chronic diseases, cirrhosis is present with increased oxidative stress that leads to an increase in reactive oxygen species, and oxygen-based molecules with high chemical reactivity that include free radicals (species with one or more unpaired electrons), such as superoxide anions O2- and nonradical species such as hydrogen peroxide (H2O2). This free radical reacts quickly with NO resulting in a decrease in NO bioavailability (Berzigotti, 2014).
    1) Ascorbic Acid (Vitamin C) is a potent natural antioxidant that is often reduced in patients with cirrhosis. Intravenous administration of high doses of vitamin C has been shown to improve endothelial dysfunction and reduce oxidative stress (Berzigotti *and* Bosch, 2014).
    2) Tetrahydrobiopterin (BH4) Cirrhosis is associated with reduced BH4 levels by decreasing the activity and expression of the synthesis key enzyme, i.e. GTP-cyclohydrolase. Furthermore, most of the BH4 is inactivated through the oxidation process. The decrease in BH4 leads to the release of eNOS thus decreasing the availability of NO. Short-term BH4 supplementation may correct the release of eNOS and become the basis of BH4 use for portal hypertension therapy (Berzigotti, 2014).
    3) Extracellular Superoxide Dismutase is an important superoxide dismutase (SOD) antioxidant enzyme that catalyzes superoxide (O2-) reactions into oxygen and hydrogen peroxide. In patients with cirrhosis, there is a decrease in expression and SOD activity. Giving recombinant human manganese superoxide dismutase (rMnSOD) has been shown to decrease portal hypertension with the added benefit of reducing liver fibrosis and enhancing liver endothelial function (Berzigotti, 2014).
    4) Fenofibrate is a peroxisome activator proliferator-that activated PPARα receptor which is a transcription factor in regulating genes related to vascular tone, oxidative stress, and fibrogenesis. Administration of fenofibrate induces a decrease in portal blood

vessel pressure by 30% and increases arterial pressure in cirrhosis (Berzigotti, 2014).

5) Resveratrol (3,5,40-trihydroxystilbene) is a polyphenol flavonoid compound found in red grapes, berries, and nuts. This substance can cause increased hepatic uptake. Besides having benefits as antineoplastic, anti-inflammatory, and anti-aggregation activity of platelets, this substance is a potent antioxidant that can have an effect on endothelial protection of blood vessels. Resveratrol lowers portal blood pressure through decreased intrahepatic resistance (Berzigotti, 2014).
6) Dark chocolate contains high levels of antioxidant cocoa flavonoids (e.g., catechin and epicatechin) which can increase the availability of NO in the systemic circulation. Dark chocolate supplementation (0.55 g/kg body weight) in liquid foods may induce a gradual reduction of increased portal blood vessel pressure after meals (Berzigotti, 2014).
7) COX-1 modulation in cirrhosis increases vasoconstrictors of COX-1 prostanoid derivatives such as thromboxane (TXA2) that are involved in elevated intrahepatic blood vessel pressure. This is especially true in conditions of lacking availability of NO as a vasodilator. COX also contributes to increasing oxidative stress and increasing the production of TXA2 (which reduces eNOS activity) and leads to an increase in O2-. Overall, this will reduce the availability of NO (Berzigotti, 2014).
   a. Rifaximine is used to prevent bacterial translocation and endotoxemia that further aggravate hyperdynamic circulation in decompensated cirrhosis patients and cause an increase in portal pressure due to increased blood vessel resistance. Therefore, the handling of bacterial translocation becomes the target of porta hypertension therapy. Rifaximin is a broad-spectrum antibiotic that is not absorbed after oral administration so it works only in the gastrointestinal tract. In patients with decompensated alcoholic cirrhosis, portal pressure decreases significantly after intestinal decontamination with rifaximin (1200 mg/day for 28 days). This parallels the decrease in endotoxin levels (Berzigotti, 2014; Garbuzenko, 2015).
   b. Antiangiogenesis actively contributes to inducing portal hypertension. Signs of neoangiogenesis, such as vascular endothelial growth factor and platelet derivative growth factor, are elevated in experimental animals with portal hypertension. Inhibition of this substance with anti-vascular endothelial growth factor and antiangiogenetic drugs significantly decreases splanchnic vasodilation and collateral formation resulting in a decrease in portal blood pressure (Berzigotti, 2014).

4 CONCLUSION

Portal hypertension is an increase in Hepatic venous pressure gradient (HVPG) above the normal value of 5 mm Hg. The goal of therapy for patients with portal hypertension is to lower blood vessel portal pressure.

Portal hypertension therapy, especialy in pharmacological management, should be able to lower blood vessel portal pressure without lowering arterial pressure, which may aggravate hyperdynamic circulation and increase the risk of renal failure. Most of the drugs often used in clinical practice are splanchnic vascular vasoconstrictors vasopressin derivatives (terlipressin), somatostatin, somatostatin analogs (octreotide and vapreotide), Nonselective β-Blocker and Carvedilol.

Some of the less commonly used drugs include Statins and Inhibitors of the Aldosterone Renin-Angiotensin System. The drugs that are still in research include etiology therapy, obesity, antifibrotic, oxidative stress-reducing drugs, rifaximin, and antiangiogenesis.

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PAGE 1

PAGE 2

PAGE 3

PAGE 4

PAGE 5

PAGE 6

PAGE 7

PAGE 8