Modern medical management of portal hypertension – primary and secondary prophylaxis of variceal bleeding in cirrhotic patients

ESSAY

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بسم الله الرحمن الرحيم

F **أَلَمْ تَرَ أَنَّ اللَّهَ أَنزَلَ مِنَ السَّمَاءِ مَاءً فَأَخْرَجْنَا بِهِ ثَمَرَاتٍ مُّخْتَلِفًا أَلْوَانُهَا وَمِنَ الْجِبَالِ جُدَدٌ بِيضٌ وَحُمْرٌ مُّخْتَلِفٌ أَلْوَانُهَا وَغَرَابِيبُ سُودٌ (٢٧) وَمِنَ النَّاسِ وَالدَّوَابِّ وَالْأَنْعَامِ مُخْتَلِفٌ أَلْوَانُهُ كَذَٰلِكَ إِنَّمَا يَخْشَى اللَّهَ مِنْ عِبَادِهِ الْعُلَمَاءُ إِنَّ اللَّهَ عَزِيزٌ غَفُورٌ (٢٨)** E

صدق الله العظيم

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ABBREVIATIONS

AASLD	:	American Association for Study of Liver Diseases
ACE	:	Angiotensin Converting Enzyme
ACG	:	American College of Gastroenterology
AFLD	:	Alcoholic Fatty Liver Disease
ALT	:	Alanine amino transferase
ARBs	:	Angiotensin Receptor Blockers
AST	:	Aspartate amino transferase
AT1	:	Angiotensin Type 1
AT-II	:	Angiotensin II
AzBF	:	Azygos Blood Flow
BPM	:	Beat Per Minute
CK	:	Creatine Kinase
CO	:	Cardiac Output
COPD	:	Chronic Obstructive Pulmonary Diseases
EBL	:	Endoscopic Band Ligation
ECM	:	Extra-Cellular Matrix
ET	:	Endothellins
GAVE	:	Gastric Antral Vascular Ectasia
GOV	:	Gastro-esophageal Varices
HBF	:	Hepatic Blood Flow
HCC	:	Hepatocellular Carcinoma
HDL	:	High Density Lipo-proteins

HMG CO-A	:	3 Hydroxy- 3 Methyl Glutaryl Co-enzyme A
HR	:	Heart Rate
HRS	:	Hepato-Renal Syndrome
HSC	:	Hepatic Stellate Cells
HVPG	:	Hepatic Venous Pressure Gradient
IGV	:	Isolated Gastric Varix
IHVR	:	Intra-hepatic Venous Resistance
ISMN	:	Isosorbid 5-Mono-Nitrate
IVC	:	Inferior Vena Cava
LDL	:	Low Density Lipo-proteins
MAP	:	Mean Arterial Pressure
NAFLD	:	Non-Alcoholic Fatty Liver Disease
NASH	:	Non-Alcoholic Steato-hepatitis
NE	:	Norepinephrine
NO	:	Nitric Oxide
NOS	:	Nitric Oxide Synthase (e: endothelial, i: induced, n: neuronal)
PHG	:	Portal Hypertensive Gastropathy
PHT	:	Portal Hypertension
PPG	:	Portal Pressure Gradient
PRA	:	Plasma Renin Activity
PT	:	Pharmaco therapy
PTFE	:	Poly Tetra-Flouro Ethylene
PV	:	Portal Vein

RAAS	:	Renin Angiotensin Aldosterone System
RCT	:	Randomized Controlled Trial
SBP	:	Spontaneous Bacterial Peritonitis
SMV	:	Superior Mesenteric Vein
SV	:	Splenic Vein
TIPS	:	Trans-jugular Intra-hepatic Porto-systemic Shunt
VLDL	:	Very Low Density Lipo-proteins
WHVP	:	Wedged Hepatic Venous Pressure

INTRODUCTION

The term portal hypertension [PHT] or, more strictly, portal venous hypertension, refers explicitly to a pathologic elevation of pressure in the veins that carry blood from the splanchnic organs (including the spleen) to the liver ***(Reuben et al., 2005).***

PHT is initiated by an increased resistance to portal blood flow and aggravated by an increased portal venous inflow. The site of increased resistance to portal blood flow is the basis for the classification of PHT: Prehepatic (e.g., portal vein thrombosis), intrahepatic (e.g., cirrhosis), and post hepatic (e.g., hepatic vein thrombosis, heart disease) ***(Bosch et al., 2007).***

Variceal bleeding, a direct consequence of PHT, is the most lethal complication of cirrhosis and accounts for approximately one-third of all deaths among patients with chronic liver disease and cirrhosis ***(Mihas et al., 2006)***.

Thus, the need to find a way to protect from bleeding and rebleeding is an everyday challenge in the field of hepatology. Oral nonselective β-blockers are recommended for the prophylaxis of patients with medium-to-large size esophageal varices that have not bled. Nonetheless, there has been some controversy as to whether esophageal band ligation should be used

instead of nonselective β-blockers due to side effects and compliance issues with these latter drugs. All patients who survive an episode of acute variceal bleeding should undergo secondary prophylaxis. Although several studies indicate that combination therapy (β-blockers and band ligation) might be better at preventing rebleeding than endoscopy or medical therapy alone, the effect of combination therapy is unknown**.** This well performed meta-analysis confirms that combination of endoscopic and drug therapy reduces overall and variceal rebleeding in cirrhosis more than either therapy alone. This is in line with the current recommendations from the American Association of Study of Liver Diseases [AASLD] and American College of Gastroenterology [ACG] ***(Cárdenas et al., 2009)***.

Yet newer drugs and modalities to reduce portal pressure with better results than both β blockers and endoscopic band ligation [EBL] are needed. This need call for a mandatory systematic review of the current medical treatments, reporting the indications & efficacy of each regimen or their combination in primary & secondary prevention of variceal bleeding. In selected cirrhotic patients, pharmacological inhibition of the angiotensin type 1 [AT1] receptor is well tolerated and induced a mild reduction of portal pressure. This hemodynamic effect might be related to liver fibrogenesis activity **(*Debernardi-Venon et al., 2007).***

Combination treatment of propranolol plus irbesartan is well tolerated in cirrhotic patients when titrating the angiotensin II antagonist in a step-up manner and it increases sodium excretion in patients with compensated or moderately decompensated cirrhosis ***(Schepke et al., 2008).***

Double-blind, randomized controlled trial [RCT] showed that 1-month simvastatin administration significantly decreased hepatic venous pressure gradient [HVPG] in patients with cirrhosis and severe PHT. Although moderate, the magnitude of this effect has potential clinical relevance ***(Abraldes et al., 2009).***

- ## Aim of work:

To provide an overview of the current knowledge on the best evidence based therapeutic options to prevent first or recurrent bleeding from esophageal varices in patients with cirrhosis. (New drugs and conventional)

- ## Methodology:

Systematic review of literature and recent papers (starting from 2006-recent) that study and concerned with PHT and primary and secondary prophylaxis of variceal bleeding, with especial concern to medical treatment and new drugs used in the prophylaxis of bleeding and rebleeding

PORTAL HYPERTENSION

Definition:

PHT is defined by a pathologic increase in portal pressure, in which the pressure gradient between the portal vein [PV] and inferior vena cava [IVC] (the portal pressure gradient [PPG]) is increased above the upper normal limit of 5 mm Hg. PHT becomes clinically significant when the PPG increases above the threshold value of 10 mm Hg (e.g., formation of varices) or 12 mm Hg (e.g., variceal bleeding, ascites). PPG values between 6 and 10 mm Hg represent subclinical PHT. ***(Bosch et al, 2007).***

It is important to mention that the rise in portal pressure is not simply a consequence of an increase in systemic venous pressure, as might occur with heart failure for example, but is intrinsically part of an increase in the pressure between the portal venous inflow to the liver and its hepatic venous outflow. Increased pressure in the hepatic veins from any cause elevates portal pressure above its normal baseline value and can cause splenomegaly and ascites. ***(Reuben et al, 2005).***

Embryology of the Portal System:-

The portal venous system originates from the two vitelline and the two umbilical veins. The vitelline veins, which drain

blood from the yolk sac, intercommunicate in the septum trasversum, at which point the liver sinusoids and lobules develop. The extrahepatic portal system develops primarily from the left vitelline vein (which is later joined by the splenic vein to form the PV), whereas the intrahepatic portal circulation originates from the umbilical veins. In addition, the left umbilical vein communicates with the venous sinus connecting with the inferior vena cava, thus allowing a large quantity of blood to bypass the liver in the fetal circulation. Soon after birth, the umbilical vein is obliterated and the normal adult circulation is established. ***(Pinzani et al, 2005).***

Anatomy of portal system:-

The PV begins at the level of the second lumbar vertebra, just behind the neck of the pancreas as an upward continuation of the superior mesenteric vein [SMV] after this vessel has been joined by the splenic vein [SV].The PV trunk receives (in some variants) the superior pancreatico-duodenal vein (with right gastro epiploic vein) and the right gastric (pyloric) veins. The left gastric (coronary) vein joins the PV at its origin 50% of the time, and it joins the splenic instead of the PV in the other 50% of subjects. Coronary vein runs upward along the lesser curvature of the stomach, where it receives some esophageal veins. **(fig.1)** ***(Pinzani et al, 2005).***

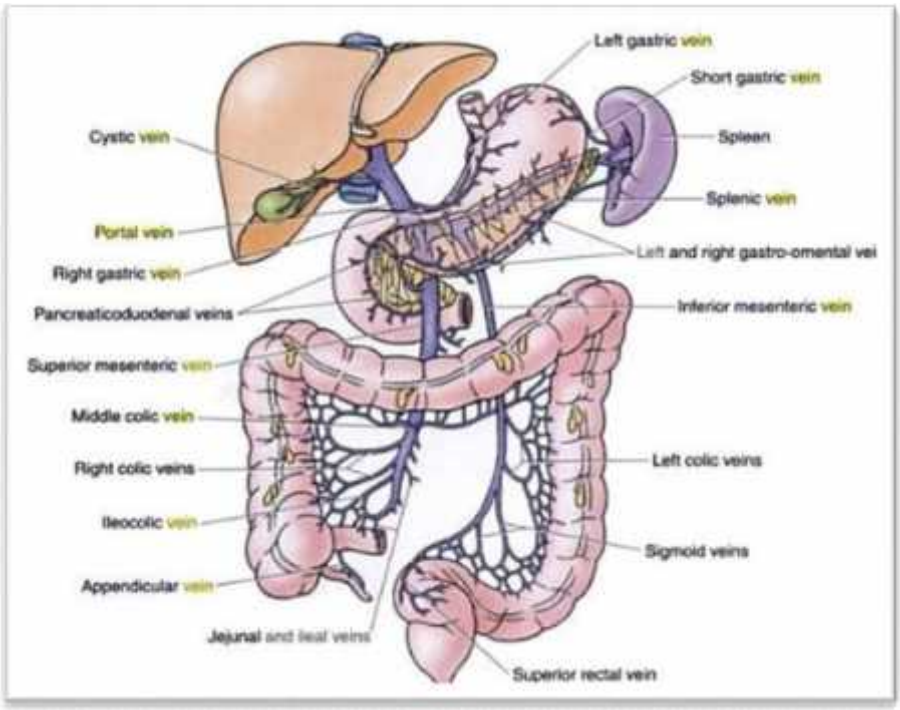

Fig. (1): Anatomy of the portal vein

The segment of the PV after the last afferent branch runs in the free edge of the lesser omentum in a plane dorsal to the bile ducts and the hepatic artery. The normal PV may measure up to 13 mm in diameter (immediately anterior to the IVC) during quite inspiration by ultrasound. Although the caliber of the SV and SMV usually increases significantly during inspiration, the PV caliber variation may be slight or absent ***(Lebrec and Moreau, 2001)***.