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HVPG as a prognostic tool in liver diseases

KEYWORDS

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BACKGROUND

Portal hypertension is characterised by increasing portal pressures resulting in an increasing gradient between splanchnic and systemic circulation. Measurement of Hepatic Venous Pressure Gradient (HVPG) is the preferred technique for determining portal pressure in present times. This method has replaced direct measurement of portal pressure. It has been proven that the values of HVPG correlate to various outcomes in patients with cirrhosis (compensated or decompensated) and ACLF. The role of HVPG continues to evolve and has been diversified in the evaluation of chronic hepatitis, hepatocellular carcinoma (HCC) and pre-transplant assessment. Measurement of HVPG the preferred technique for determining portal pressure has replaced direct measurement of portal pressure.[1] WHVP is measured by occluding one of the main hepatic veins (mostly right hepatic vein).[2] WHVP is a measure of hepatic sinusoidal pressure, not of portal pressure thus WHVP will be an underestimation of portal venous pressure (PVP) if a pre-sinusoidal resistance is present. In the normal liver WHVP is slightly lower (by ~1 mmHg) than portal pressure, due to pressure equilibration through the interconnected sinusoids.[3] WHVP gives an accurate estimate of portal pressure, as has been demonstrated both for alcoholic and viral cirrhosis.[4] FHVP is measured in unoccluded hepatic vein. It is the FHVP that should be used to calculate the hepatic venous pressure gradient and not the right atrial pressure because HVPG calculated with right atrial pressure shows a worse correlation with clinical outcomes.[5] HVPG is better than WHVP and FHVP because they are affected by intra-abdominal pressure, but the gradient (HVPG) is not.[6]

MATERIALS AND METHODS

We evaluated the role of HVPG as a predictor of complications and outcomes in patients with liver disease (ACLF and cirrhosis).

Ethical Consideration

We obtained the necessary approval to conduct the study from the Institutional Ethics Committee of Army Hospital (Research and Referral) Delhi Cantt., India. The participants were given a full explanation about the purpose of the study and that the participation was optional. Consent of the patients was taken prior to enrolment to the study.

Investigations

HVPG was performed within 3 days of hospitalization (i.e. approximately within 4 weeks of onset of acute event) and after an overnight fast with full aseptic precautions. Under local anesthesia, a central venous catheter (7F, Arrow; Arrow International, Reading, PA) was placed in the right internal jugular vein under fluoroscopic guidance technique by using the Seldinger technique. The HVPG was measured by the standard technique. All measurements were performed in triplicate and if the difference between the two HVPG readings was more than 1 mmHg, all of the readings were discarded, and a fresh set of measurements were carried out.

Measurement of HVPG

Fasting for 8 hours is required for the preparation of HVPG measurement. Equipment such as electrocardiography monitor, O_2 saturation monitor, pressure recorder, pressure transducer, fluoroscopy, and ultrasonography are required. In addition, 6 Fr balloon catheter, puncture needle, vascular introducer, contrast dye and local anaesthesia are required for the proper measurement. Ante-cubital, femoral or right jugular veins are various routes for insertion of catheter in HVPG measurement. Right jugular vein is most commonly used. A 6 Fr balloon catheter is placed in the right hepatic vein through a right jugular vein puncture and FHVP is measured. The WHVP is measured by inflation of the balloon catheter in the right hepatic vein. Later, the HVPG is determined by subtracting the FHVP from the WHVP

Statistical Analysis

The statistical analysis was performed using SPSS version 20. The clinical profile of patients was analyzed by chi-square test for qualitative variables and student t test / One way ANOVA for quantitative variables. A 5% probability level was considered as statistically significant i.e., $p<0.05$.

RESULTS

The study was carried out at the Department of Gastroenterology at Army hospital (Research and Referral) between Jun 2013 and Jan 2015 with an aim to evaluate the role of HVPG as a predictor of complications and outcome in patients of cirrhosis and ACLF

Hepatic Venous Portal Gradient

HVPG was measured in all patients of the three groups. The mean+/-SD HVPG was 12.3 + 7.5mmHg which was significantly higher than the normal gradient. It was also noted that the HVPG was significantly higher in the ACLF 13.7+6.8mmHg and decompensated cirrhotics 14.4 + 7 mmHg as compared to compensated cirrhotic group with HVPG of 8.8 +2.1 mmHg (P=<0.001)

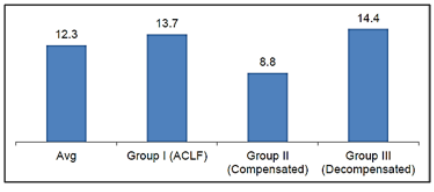

Figure 1 Average HVPG in patients

The mean+/-SD HVPG was significantly higher than the normal gradient. It was also noted that the HVPG was significantly higher in the ACLF and decompensated cirrhotics as compared to compensated cirrhotic group (P=<0.001).

HVPG and Etiology

Etiology had an impact on HVPG in our study. Patients with viral or

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alcoholic etiologies had a higher HVPG than those with autoimmune or cryptogenic cirrhosis. The mean+/-SD HVPG for the various etiologies were noted to be 11.6+8mmHg (for viral hepatitis), 13.23+6.2 mmHg (for alcoholic liver disease), 8.0 + 3.2 (for autoimmune hepatitis) and 7.0+ 3.1 (for cryptogenic cirrhosis). Even for independent sub groups it was evident that patients of alcoholic or viral etiologies had a significantly higher HVPG as compared to their counterparts in other sub groups (Figure.2). But when analysed within any particular etiology, a significant difference of HVPG between ACLF and decompensated cirrhosis was not present (p <.729).

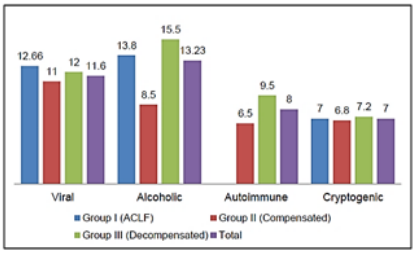

Figure 2. HVPG and Etiology

When pressure gradients of compensated cirrhotics was analysed and compared against the other two sub groups, the pressure gradients of compensated cirrhotics was significantly lower. (p=.012)

Comparison of HVPG against other prognostic scores

MELD is a marker of synthetic function of the liver and the state of other organ involvement in a case of chronic liver disease. It however is not a much validated predictor of portal pressures and GI bleed. When plotted on a scatter graph MELD and HVPG showed a good correlation throughout the range of MELD. With rising values in MELD the corresponding values of HVPG were also rising similar graph was plotted for CTP and HVPG. It was interesting to note that at lower values of CTP (CHILD A) the HVPG was consistently low, but as the CTP scores continued to progress from CHILD B to CHILD C the interdependency of CTP and HVPG grew weaker.

The higher CTP scores had a very wide range of HVPG values (6 – 28 mmHg) whereas the lower CTP scores (CHILD A) had a narrow range of HVPG (5 – 15 mmHg). A similar plot was made for SOFA against HVPG and a similar observation (Figure 3)

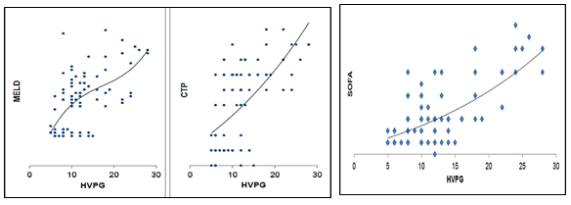

Figure 3. Comparison MELD, CTP and SOFA with HVPG

MELD and HVPG showed a good correlation throughout the range of MELD. The higher CTP scores had a very wide range of HVPG values (6 – 28 mmHg) whereas the lower CTP scores (CHILD A) had a narrow range of HVPG (5 – 15 mmHg).

HVPG for Mortality and GI Bleed

The role of HVPG in predicting GI bleed or short term mortality in ACLF and decompensated liver disease. The HVPG values of decompensated cirrhotics were not very different from ACLF patients. Amongst the non survivors it was 22.3+5.37mmHg and within survivors it was 12.5+3.4 mmHg. (p = 0.502). The occurrence of GI bleed also was associated with higher HVPG in patients of ACLF as well as decompensated cirrhotics.

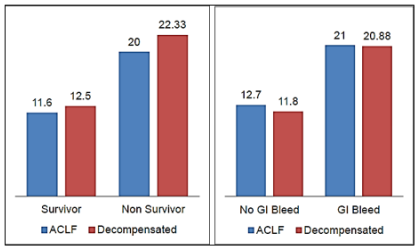

Figure 4 Mortality and GI Bleed

Among patients with ACLF the mean+/-SD HVPG of survivors was significantly lower than non survivors. The mean+/-SD pressures in the patients of ACLF who had a bleed in the hospital was higher than the ones who did not and this was also noted amongst the patients of decompensated cirrhosis.

WHVP; Wedged Hepatic Venous Pressure, FHVP; free hepatic venous pressure, MELD; Model for End-Stage Liver Disease, CTP; Child-Turcotte-Pugh

DISCUSSION

The main utility of HVPG has been in classification of Portal Hypertension according to the site of obstruction as Pre-hepatic (involving the splenic, mesenteric, or portal veins), Intra-hepatic (parenchymal liver diseases) and Post-hepatic (diseases involving the hepatic venous outflow).[7]

Portal vein thrombosis is the most common cause of pre-hepatic portal hypertension. Intra-hepatic causes of portal hypertension are the most common cause of portal hypertension, liver cirrhosis being responsible for approximately 90% of cases of portal hypertension.[7] Pre-sinusoidal portal hypertension shows normal WHVP and FHVP values, as is the case for non-cirrhotic portal hypertension and hepatic granulomatosis (early stages of primary biliary cirrhosis (PBC) and schistosomiasis, sarcoidosis, tuberculosis). Sinusoidal portal hypertension gives rise to increased WHVP and normal FHVP and is found in most chronic liver diseases, except for PBC.[7] In post-sinusoidal portal hypertension, both the WHVP and FHVP are increased, as seen in Budd-Chiari syndrome (hepatic vein thrombosis). Causes of post-hepatic portal hypertension include heart failure, constrictive pericarditis, or occlusion of the supra-hepatic part of inferior vena cava.[7]

HVPG in Chronic hepatitis and cirrhosis

The use of the HVPG for the measurement of portal pressure is well established in chronic liver disease.[8] The main cause of morbidity and mortality in chronic viral hepatitis is development of portal hypertension due to development and progression of cirrhosis. Changes in HVPG are not only better than standard parameters for staging chronic hepatitis but also evaluating the response of the disease to antiviral treatment. HVPG offers a much better reflection of liver parenchymal function in a dynamic way than does liver biopsy.[9] HVPG correlates with the degree of histological liver fibrosis in patients with Hepatitis B virus-related and Hepatitis C virus-related chronic hepatitis.[10] Several studies have compared HVPG measurements taken before and after treatment in patients with chronic hepatitis C.[11]

Rincon et al. reported that in patients with advanced (METAVIR stage F3 or F4) chronic hepatitis C significant reduction in HVPG is detected following antiviral therapy.[11] HVPG measurements might be the best way to evaluate the progression or regression of cirrhosis in patients with advanced chronic hepatitis.[12] HVPG is also important in patients with decompensated cirrhosis, where it has a predictive role about the risk of death during follow-up.[13, 14] The HVPG is a strong and independent marker of outcomes in compensated and decompensated cirrhosis.[12]

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HVPG in Alcoholic hepatitis

Acute alcoholic hepatitis (AAH) is a severe condition with a high mortality rate. It is associated with higher HVPG values. In a study of 60 patients with severe AAH (Maddrey discriminant function value of >32), multivariate analysis revealed that HVPG of greater than 22mmHg (measured within 8 days of admission), a MELD score of greater than 25 points, and encephalopathy were independent predictors of in-hospital mortality. 48% of patients had an HVPG greater than 22mm Hg.[15] **The in-hospital mortality rate in these patients was 66%, suggesting that HVPG could be a valuable tool to risk-stratify patients with severe AAH.[15]**

Studies of HVPG in ACLF

Portal hemodynamics of patient with ACLF is different from patients with compensated and decompensated liver cirrhosis, partially because of circulating mediators. While patients with ACLF with small varices had HVPG values (13.2 ± 5.5 mm Hg) comparable with those of compensated cirrhotic patients, those with large varices had HVPG values comparable with those of decompensated cirrhotic patients (18.2 ±6.5 mm Hg).[16]

A study by Garg et al. and colleagues showed that ACLF patients have raised portal pressure and it rises in them rather very acutely without giving adequate time for collateral vessels to develop. These patients are therefore at a higher risk of portal hypertension-related complications with a high risk of mortality. In cirrhotic patients, the size of esophageal varices has been shown to correlate with the risk of variceal bleeding, but the risk is only about 6–10% per year in patients with large varices and about 30% in those with large and high risk varices. [17] **It has been observed that the mean arterial pressure (MAP) and systemic vascular resistance (SVR) were lower in the ACLF and decompensated cirrhosis patients when compared with compensated cirrhotic patients.**

CONCLUSION

HVPG is the best surrogate marker in portal hypertension. In addition, it can predict the development of varices, ascites, encephalopathy, or other complications. A reduction in the HVPG is related to a reduction in the incidence of varices and variceal haemorrhage. Therefore, measurement of HVPG besides monitoring hemodynamic effects will mainly assess all fields of chronic liver diseases.

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