SPECTRUM OF COLONIC MUCOSAL ABNORMALITIES IN PATIENTS WITH CIRRHOSIS AND PORTAL HYPERTENSION : AN ENDOSCOPIC STUDY

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Certificate

This is to certify that this dissertation entitled **"SPECTRUM OF COLONIC MUCOSAL ABNORMALITIES IN PATIENTS WITH CIRRHOSIS AND PORTAL HYPERTENSION : AN ENDOSCOPIC STUDY",** submitted by **Dr.D. Sasi Anand** to the faculty of Medical Gastroenterology, The Tamilnadu Dr.MGR Medical University, Guindy, Chennai-600032, in partial fulfillment of the requirement for the award of DM Degree, Branch IV (Medical Gastroenterology) is a bonafide work carried out by him under my direct supervision and guidance.

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INTRODUCTION

Portal hypertension (PHT) is an important complication of chronic liver disease of any etiology . One of the most significant clinical consequences of portal hypertension in cirrhotic patients is the development of gastroesophageal varices, portal hypertensive gastropathy (PHG) and gastric antral vascular ectasia (GAVE). These vascular lesions are considered to be a significant source of upper gastrointestinal bleeding in patients with portal hypertension.

Over the past few years, it has been observed that not only the stomach but the entire gastrointestinal tract, with its venous drainage through the portal venous system, is involved in patients with portal hypertension. Involvement of the duodenum , the small intestine , and the colon have all been described. Only a few studies, however, have investigated the colon in patients with portal hypertension.

Colorectal mucosal lesions in patients with portal hypertension is termed as portal hypertensive colopathy (PHC). These are thought to be important causes of lower gastrointestinal hemorrhage, although the clinical importance of these lesions in patients with portal hypertension is not well

established. The features of PHC are not well defined but include multiple vascular appearing lesions (telangiectasias, cherry red spots and angiodysplasia like lesions), colitis- like abnormalities (granularity, erythema, edema, friability), colorectal varices, or a combination of these findings. The diagnostic criteria and clinical significance of this condition is confusing. This may be partially due to imprecise terminology, lack of uniform endoscopic descriptions, interobserver variability and the absence of distinctive histopathologic features.

The effect of endoscopic sclerotherapy (EST) as well as endoscopic variceal band ligation (EVL), on PHG is well known. In most studies an increased incidence of PHG has been noted in patients who have undergone EST and EVL. There are few studies which suggest that variceal obliteration may result in an increase in the incidence of anorectal varices and portal hypertensive colopathy. In more recent years, EVL has virtually replaced EST as the treatment option for esophageal varices. However, there are very few studies which have investigated the effect of EVL on the colonic mucosa in patients with portal hypertension.

In this study, we evaluated the prevalence of colonic mucosal changes in patients with chronic liver disease and portal hypertension before and after endoscopic variceal obliteration and its clinical significance

REVIEW OF LITERATURE

Cirrhosis is a gradually developing, chronic disease of the liver. It is the irreversible consequence and final stage of various liver disease of different etiology or the result of long term exposure to noxious agents. Aretaeus (2nd century AD) coined the term "skirros", because he thought that inflammation of the liver led to its hardening (skirros).

The first accurate report on cirrhosis was given by R.T.H. Laennec (1819). Because of the yellow colour of the liver (kirros), he coined the term cirrhosis. The morphological changes depend on the cause and stage of cirrhosis. Accordingly, there is a wide spectrum of morphological findings and clinical symptoms. The variation of this disease range from symptom free conditions, non characteristic complaints and different laboratory findings through to life threatening complications.

Cirrhosis of liver can be classified either etiologically or morphologically. The etiological classification is based on the underlying cause which includes alcohol, hepatitis B and hepatitis C infections, metabolic disorders like Wilson disease, nonalcoholic fatty liver disease and and also due to autoimmune hepatitis. When no cause is found it is called as cryptogenic cirrhosis. Morphological classification is based on the size of the nodules. It could be micronodular if the nodules are less than 3mm,

macronodular if they are more than 3mm and mixed type if both are found. The mixed type is the transition form from micronodular to macronodular cirrhosis.

Cirrhosis of the liver is a disease found all over the world, affecting all races, age groups and both sexes. The increasing mortality rate runs parallel to regional alcohol consumption. This correlation between alcohol consumption and mortality as well as morbidity due to cirrhosis applies equally to men and women. The slight decrease in mortality in some countries observed during the past 10 -15 years may be due to more effective prophylaxis and improved treatment options for complications.

Portal hypertension is one of the salient features of cirrhosis. Cirrhosis of the liver accounts for approximately 90% of cases of portal hypertension.

PORTAL HYPERTENSION

Definition: A clinical syndrome defined by a pathologic increase in the portal venous pressure, in which the portal pressure gradient is >5 mmHg (difference between the pressure of the portal vein and that of the inferior

vena cava). The portal vein is 5- 8 cm long with a diameter of 1.2 ± 0.2 (or 0.97) cm [1.]

Classification of Portal Hypertension

Portal hypertension is classified according to the localization of the flow resistance. Increases in pressure in the portal vascular system are rapidly transferred to the preceding vascular sections, since the portal vein does not possess any venous valves. Depending on whether the localization lies before, within or beyond the liver, the portal hypertension is broken down into prehepatic, intrahepatic and posthepatic blocks. The intrahepatic form is further subdivided into a presinusoidal, sinusoidal and postsinusoidal rise in resistance.

NON-PARENCHYMATOUS PORTAL HYPERTENSION

1. PREHEPATIC PORTAL HYPERTENSION

2. INTRAHEPATIC PORTAL HYPERTENSION

    A. PRESINUSOIDAL BLOCK

PARENCHYMATOUS PORTAL HYPERTENSION

B. SINUSOIDAL BLOCK

C. POSTSINUSOIDAL BLOCK

3. POSTHEPATIC PORTAL HYPERTENSION

Pathophysiology of Portal Hypertension

Portal Pressure Gradient (PPG) is the result of the interaction between the portal blood flow and the vascular resistance to the flow. This relationship is defined by Ohm's law in the following equation:

$\Delta P = Q \times R$

in which ΔP is the PPG (the difference between the portal pressure and the IVC pressure), Q is the blood flow within the entire portal venous system (which in portal hypertension includes the portal–systemic collaterals), and R is the vascular resistance of the entire portal venous system. It follows that portal pressure may be increased by an increase in portal blood flow, an increase in vascular resistance, or a combination of both [2]. It is well established that in cirrhosis, the primary factor leading to portal hypertension is an increased resistance to portal blood flow. An

increased portal venous inflow maintains and exacerbates portal hypertension. This component of increased blood flow becomes especially important in advanced stages.

Increased Vascular Resistance to Portal Blood Flow

Increased resistance to portal blood flow is the primary factor in the pathophysiology of portal hypertension and may occur at any site within the portal venous system. In cirrhosis, increased intrahepatic vascular resistance is thought to be mainly in the hepatic sinusoids [3]. For many years, the increased intrahepatic vascular resistance was thought to be a fixed, mechanical consequence of architectural distortion of the hepatic microcirculation by fibrosis, scarring, and nodules. In addition, careful pathologic studies have suggested that thrombosis of medium and large portal and hepatic veins is a frequent occurrence in cirrhosis and that these events may be important in causing a progression of cirrhosis and worsening of portal hypertension [4] . However, recent studies have demonstrated that in addition to the increased resistance caused by the morphologic changes of chronic liver diseases, a dynamic component of increased resistance is present that represents active contraction of the contractile elements in the liver. These elements constrict in a reversible and graded manner in response to several agonists, thereby further increasing the intrahepatic resistance [5]. It

has been claimed that this dynamic component may represent up to 40% of the increase in intrahepatic vascular resistance.

The contractile elements of the hepatic vascular bed are located at a sinusoidal level and at extrasinusoidal sites [6,7,8]. They include smooth muscle cells of the intrahepatic vasculature (i.e., small portal venules in portal areas) [6]; activated hepatic stellate cells, which are located in the perisinusoidal space of Disse and have extensions that wrap around the sinusoids[7]; and hepatic myofibroblasts, which are abundant in the fibrous tissue in and around cirrhotic nodules. Contraction of hepatic myofibroblasts may increase intrahepatic resistance by compressing venous shunts in the fibrous septa. It is now clear that vasoactive mediators, either vasoconstrictors or vasodilators, modulate intrahepatic vascular resistance in both the healthy and the cirrhotic liver. An increased production of vasoconstrictors and an exaggerated response of the hepatic vascular bed to these agents, as well as an insufficient release of vasodilators, together with an impaired vasodilatory response of the hepatic vascular bed, are the mechanisms that have been implicated in the pathogenesis of the dynamic component of the increased intrahepatic resistance of the cirrhotic liver [3].

Increased Production of Vasoconstrictors

Endothelins : *Endothelins* (*ETs*) are a family of homologous 21 amino acid vasoactive peptides (ET-1, ET-2, and ET-3) that are thought to play a major role in modulating hepatic vascular tone in cirrhosis [9]. The biologic properties of ETs are mediated essentially by two major ET receptors, ET-A and ET-B. The ET-A receptor shows a high affinity for ET-1 and mediates constriction; the ET-B receptor has equal affinity for ET-1 and ET-3. Activation of ET-B receptors located on the vascular smooth muscle cells promotes vasoconstriction, whereas activation of ET-B receptors located on endothelial cells promotes vasodilatation, which is mediated by enhanced nitric oxide (NO) and prostacyclin produced by the endothelial cell. Patients with liver cirrhosis have increased circulating plasma levels of ET-1 and ET-3 [10]. Endothelial cells, hepatic stellate cells (in their activated phenotype), and bile duct epithelial cells are the major intrahepatic sources of ET-1. ET-1 increases portal perfusion pressure by increasing intrahepatic resistance in isolated, perfused normal livers and carbon tetrachloride–induced cirrhotic livers. Although some experimental studies reported a slight reduction of portal pressure in cirrhotic animals after the administration of ET antagonists [11, 12], this was not confirmed by other studies [13]. Therefore, the role of ETs in increasing the vascular tone in cirrhosis remains unsettled.

Other vasoconstrictive factors are involved in the regulation of hepatic vascular tone. Studies in perfused cirrhotic livers have shown that *norepinephrine, angiotensin II*, and *vasopressin*, three circulating vasoactive factors whose levels are usually elevated in cirrhosis, increase intrahepatic vascular resistance [14,15].

Endothelial Dysfunction in Cirrhosis

In normal conditions, the endothelium is able to generate vasodilator stimuli in response to increases in blood volume, blood pressure, or vasoconstrictor agents in an attempt to prevent or attenuate the concomitant increase in pressure. In several pathologic conditions there is an impairment in this endothelium-dependent vasodilatation, called endothelial dysfunction [16,17]. The hepatic vascular bed of cirrhotic livers also exhibit endothelial dysfunction [18]. Indeed, studies performed both in patients with cirrhosis and in experimental models have shown that, contrary to what happens in normal livers, the cirrhotic liver cannot accommodate the increased portal blood flow caused by the postprandial hyperemia, which determinesss an abrupt postprandial increase in portal pressure [19]. This is important because such repeated brisk increases in portal pressure and portal– collateral blood flow in response to meals and other physiologic stimuli are thought to be a major

determinant of the progressive dilatation of the varices in patients with cirrhosis [3].

Insufficient Release of Hepatic Vasodilators

Nitric oxide : The role of NO in modulating intrahepatic vascular resistance is a subject of considerable interest. NO is a powerful endogenous vasodilator generated in several tissues by NO synthases from the amino acid L-arginine. It is the natural ligand for soluble guanylate cyclase and is responsible for an increase in the levels of cyclic GMP, the final agent responsible for the relaxation of the vascular wall through the extrusion of cytosolic Ca2+. NO blockade has been shown to increase portal perfusion pressure in isolated perfused rat livers. In addition, the hepatic response to norepinephrine is markedly enhanced after NO inhibition, a finding that further suggests a role for NO in modulating hepatic vascular tone in normal conditions [20]. In the cirrhotic liver, the synthesis of NO is insufficient to compensate for the activation of vasoconstrictor systems frequently associated with cirrhosis. This occurs despite a normal expression of endothelial nitric oxide synthase (eNOS) mRNA and normal levels of eNOS protein [18,21]. The decreased activity of hepatic eNOS in cirrhosis is due in part to increased expression of caveolin [22]. This insufficient hepatic NO

generation plays a major role in increasing intrahepatic vascular resistance in cirrhosis, thereby worsening portal hypertension.

Carbon monoxide : A role for carbon monoxide (CO), a by-product of heme group oxidation by heme oxygenases (HOs), as an important modulator of intrahepatic vascular tone has been suggested. CO, although less potent than NO, also activates guanylate cyclase and thereby promotes smooth relaxation. The inhibition of CO production increases portal resistance in normal livers [23]. Heme oxidation is catalyzed by two different enzymes, HO-1 and HO-2. In normal conditions, CO is produced in the liver by the constitutive isoform (or HO-2).However, in several stress conditions, such as endotoxemia and hemorrhagic shock, the inducible isoform (or HO-1) is formed. In this situation, the inhibition of HOs with specific agents leads to a much greater increase in portal–hepatic resistance than is seen in normal, unstimulated livers [24]. In addition, there is a complex interaction between the NO and CO systems. NO has been shown to induce HO-1 expression and, therefore, CO synthesis. On the other hand, CO may inhibit the NO-mediated production of cyclic guanylate cyclase monophosphate. Therefore, an increased expression of HO-1 in cirrhosis suggests that CO may play a role in the hepatic circulatory disturbances found in liver cirrhosis.

Splanchnic Vasodilatation

An increased portal venous inflow is characteristically observed in advanced stages of portal hypertension and is the result of marked arteriolar dilatation in the splanchnic organs draining into the portal vein. The increased blood flow contributes to the portal hypertensive syndrome [3]. Different mechanisms have been suggested to explain the observed hemodynamic abnormality, which likely represents a multifactorial phenomenon involving neurogenic, humoral, and local mechanisms. Initial studies focused on the potential role of increased levels of circulating vasodilators. Many candidate substances were proposed, most of them being vasodilators of splanchnic origin that undergo hepatic metabolism and accumulate in the systemic circulation when hepatic uptake is reduced in liver disease or during portosystemic shunting.

Glucagon : Glucagon is probably the humoral vasodilator for which most evidence has been accumulated to indicate a significant role for it in splanchnic hyperemia and portal hypertension. Many studies have demonstrated that plasma glucagon levels are elevated in patients with cirrhosis and experimental models of portal hypertension. Hyperglucagonemia results, in part, from a decreased hepatic clearance of glucagon, but more importantly from an increased secretion of glucagon by

pancreatic α cells [25]. The support for a role of glucagon in modulating splanchnic blood flow comes from physiologic studies showing that in rats with experimental portal hypertension, normalizing circulating glucagon levels by administering glucagon antibodies or infusing somatostatin partially reverses the increase in splanchnic blood flow, a response that can be specifically blocked by the concomitant infusion of glucagon [26,27]. Conversely, other studies have shown that increasing circulating glucagon levels in normal rats to values similar to those observed in portal hypertension causes a significant increase in splanchnic blood flow. On the basis of these studies, it has been suggested that hyperglucagonemia may account for approximately 30% to 40% of the splanchnic vasodilatation of chronic portal hypertension. Glucagon may promote vasodilatation by a dual mechanism: Relaxing the vascular smooth muscle and decreasing its sensitivity to endogenous vasoconstrictors, such as norepinephrine, angiotensin II, and vasopressin [28,29]. The role of glucagon in the splanchnic hyperemia of portal hypertension provides a rationale for the use of somatostatin and its synthetic analogs to treat portal hypertension [30].

Endocannabinoids : Recent data suggest a role for endocannabinoids in the hyperdynamic circulation of portal hypertension [31,32.]

Nitric oxide : Experimental studies of specific NO inhibitors have shown that NO is involved in the regulation of splanchnic and systemic hemodynamics in portal hypertensive and control animals[33,34]. In addition, NO inhibition has been shown to reverse the vascular hyporesponsiveness to vasoconstrictors that is characteristic of portal hypertension and is thought to contribute to systemic and splanchnic vasodilatation [35]. The finding in patients with cirrhosis of increased serum and urinary concentrations of nitrite and nitrate, which are products of NO oxidation, also supports a role for NO in the genesis of the circulatory disturbances of portal hypertension [36]. The increased production of NO is due both to an increased expression and an increased activity of eNOS[37.38]. Factors likely to activate the constitutive NO synthase include shear stress, circulating vasoactive factors (e.g., ET, angiotensin II, vasopressin, and norepinephrine) and overexpression of the angiogenic factor vascular endothelial cell growth factor (VEGF) [39,40].

Prostaglandins : Several studies support a role for prostaglandins in the hyperdynamic circulation in portal hypertension [41,42,43,44].

Portosystemic Collateral Circulation

The development of portal–collateral circulation is one of the main complications of portal hypertension. Formation of collaterals is a complex process involving the opening, dilatation, and hypertrophy of preexisting vascular channels [45]. Collaterals develop in response to the increased portal pressure. A minimum HVPG threshold of 10 mm Hg should be reached for the development of portosystemic collaterals and esophageal varices [46,47,3]. In addition to the increased portal pressure, recent studies have shown that formation of portosystemic collateral vessels in portal hypertension is influenced by a VEGF dependent angiogenic process and can be markedly attenuated by interfering with the VEGF/VEGF receptor-2 signaling pathway [39,40]. These studies have opened a new perspective in the understanding of the pathophysiology of portal hypertension, with potential clinical relevance, because these studies indicate that manipulation of the VEGF may be of therapeutic value. The collateral circulation may carry as much as 90% of the blood entering the portal system. In this circumstance, the vascular resistance of these vessels becomes a major component of the overall resistance to portal blood flow and, therefore, may be important in determining portal pressure. In addition, although it was traditionally thought that the hyperdynamic splanchnic circulatory state associated with

portal hypertension was the consequence of active splanchnic vasodilatation, recent data suggests that the increased neovascularization in splanchnic organs plays an important role in allowing the increase in splanchnic blood inflow [40]. The elements that modulate collateral resistance are not well known. Studies performed in perfused portosystemic collateral beds suggest that NO may play a role in the control of portal collateral vascular resistance [48]. This may be the mechanism by which isosorbide-5-mononitrate (IMN) and nitroglycerin (NTG) reduce collateral resistance in patients with cirrhosis. Vasoconstrictive agents (including vasopressin and nonselective β-blockers) may significantly increase the collateral resistance. The increase in portal collateral resistance brought about by these agents attenuates the reduction in portal pressure achieved by reducing the splanchnic blood flow.

Esophageal Varices

Esophageal varices are present in approximately 40% of patients with cirrhosis and in as many as 60% of patients with cirrhosis and ascites [49]. In cirrhotic patients who do not have esophageal varices at initial endoscopy, new varices will develop at a rate of approximately 5% per year. In patients with small varices at initial endoscopy, progression to large varices occurs at a rate of 10% to 15% per year and is related predominantly to the degree of

liver dysfunction [50]. On the other hand, improvement in liver function in patients with alcoholic liver disease who abstain from alcohol is associated with a decreased risk, and sometimes even disappearance, of varices [51].

Up to 25% of patients with newly diagnosed varices will bleed within two years. The best clinical predictor of bleeding appears to be variceal size. The risk of bleeding in patients with varices less than 5 mm in diameter is 7% by two years, and the risk in patients with varices greater than 5 mm in diameter is 30% by two years (50). Even more important, however, is the HVPG because the risk of bleeding is virtually absent when the HVPG is below 12 mm Hg [52]. Nevertheless, measurement of HVPG is not routinely performed in clinical practice to assess bleeding risk. The prognosis for variceal bleeding in patients with cirrhosis has improved since the 1980s. Initial treatment is associated with cessation of bleeding in approximately 90% of patients [50]. Approximately one half of patients with a variceal bleed stop bleeding spontaneously because hypovolemia leads to splanchnic vasoconstriction, which results in a decrease in portal pressure. Excessive transfusions may, in fact, increase the chance of rebleeding. Active bleeding at endoscopy, a lower initial hematocrit value, higher serum aminotransferase levels, higher Child class, bacterial infection, an HVPG greater than 20 mm Hg, and portal vein thrombosis are associated with

failure to control bleeding at five days [50,53.] Of patients who have stopped bleeding, approximately one third will rebleed within the next six weeks. Of all rebleeding episodes, approximately 40% will take place within five days of the initial bleed. Predictors of rebleeding include active bleeding at emergency endoscopy, bleeding from gastric varices, hypoalbuminemia, renal insufficiency, and an HVPG greater than 20 mm Hg. The risk of death with acute variceal bleeding is 5% to 8% at one week and about 20% at six weeks [50].

Gastric Varices

Gastric varices typically occur in association with more advanced portal hypertension. Bleeding is thought to be more common in patients with GOV2 and IGV1 than in those with other types of gastric varices; in other words, bleeding is more common from fundal varices than from varices at the gastroesophageal junction. Whereas intraesophageal pressure is negative, intra-abdominal pressure is positive, and the transmural pressure gradient across gastric varices is smaller than that across esophageal varices. Gastric varices, however, tend to be larger in diameter than esophageal varices.

Gastric varices are supported by gastric mucosa, whereas esophageal varices tend to be unsupported in the lower third of the esophagus.

Therefore, gastric varices are likely to bleed only when they are large, as demonstrated in a study in which larger gastric varices (greater than 5 to 10 mm in diameter) were more likely to bleed than smaller ones [54]. Although gastric varices have been thought to bleed less frequently than esophageal varices, the bleeding rates probably are comparable if patients are matched for the severity of cirrhosis (CTP score).[In contrast with esophageal varices, bleeding from gastric varices has been described with an HVPG less than 12 mm Hg [55,56]. Gastric varices in continuity with esophageal varices may regress following treatment of the esophageal varices. When gastric varices persist despite obliteration of esophageal varices, the prognosis is poorer, probably because of the severity of liver disease.

Anorectal varices

Blood from the haemorrhoidal venous plexus passes via the azygous superior rectal vein into the inferior mesenteric vein and thereafter into the portal vein. By contrast, the paired middle rectal vein and inferior rectal vein discharge their blood via the iliac vein into the inferior vena cava. In portal hypertension, anorectal varices are found in the region of the rectum, the anal canal and the external anal region. • Haemorrhoids are distended and dislocated cavernous bodies in the rectum, which have no connection to the portal venous system. • Although haemorrhoids and anorectal varices are

two different clinical pictures, it is quite possible for them to occur simultaneously. The frequency of anorectal varices (40 - 80%) is dependent upon the extent and duration of portal hypertension. The bleeding tendency is low (7 - 14%). However, there have also been reports of massive haemorrhages. [57]

MUCOSAL CHANGES IN PORTAL HYPERTENSION

PORTAL HYPERTENSIVE GASTROPATHY (PHG) :

The hallmarks of the lesions in PHG are ectatic vessels in the mucosa and submucosa with insignificant inflammatory cellular infiltrate [59]. Its prevalence among portal hypertensive patients ranges from 7% to 41% [60]. In the largest study on the natural history of PHG , the overall prevalence of this condition in patients with cirrhosis was 80 % [61].

The mechanisms involved in the pathogenesis of PHG have not been fully elucidated, yet chronic increase in the portal pressure is a prerequisite for its development [59]. Several factors with varying degrees of involvement, are implicated in the mechanism of PHG e.g. neurohumoral or paracrine substances, hypervolemia, meals, tissue hypoxia and in certain cases hepatocelluar insufficiency. The gastric mucosal blood flow state is debatable . Decrease in blood flow to the mucosa and increased blood flow to the submucosa, muscle, and serosal layers have been documented in

PHG. Moreover , a higher hemokinetic stress in severe PHG cases than in mild cases or controls is proved by using endoscopic laser Doppler flowmetry.

Many trials have evaluated the portal hypertensive mucosa in relation to many internal and external factors. It is worth to mention the damaging effects proved by the decreased gastric mucosal prostaglandin E2 generation in PHG. Sarin et al. has confirmed that PHG is greatly influenced by the severity of liver disease [62]. Conversely, Primignani et al. suggests that the correlation is weak [61].

Studying the impact of variceal eradication by sclerotherapy or ligation (EVS or EVL) on PHG revealed the whole spectrum of probabilities. Sarin et al. reported that EVS is incriminated in worsening PHG as compared to EVL. Although patients in this study were of a variable spectrum of liver disease (cirrhosis, fibrosis, extra-hepatic portal vein obstruction and Budd-Chiari cases), yet it had the most prolonged duration of follow up (23.2 +/- 3.4 months) .Other studies have flipped the coin, incriminating EVL as compared to EVS [62,63]. While Hou et al. didn't find any significant difference between either of EVL and EVS on PHG [64].

The identification of endoscopic lesions of PHG allowed the development of a reproducible classification defining mild and severe pictures as well as the conduction of natural history studies [64]. The elementary lesions in PHG are mosaic like pattern, red point lesion, cherry red spots and black brown spots. According to the New Italian Endoscopic Club, in mild PHG the gastric mucosa often looks reddened and edematous with a snakeskin or mosaic pattern. Severe PHG is defined by cherry red spots, which are typically very friable and can actively bleed during endoscopy. Such changes are typically localised to the fundus or corpus of the stomach. There is no specific histology nor correlation between the endoscopic and the histologic features in PHG. Ectasia and sclerosis of the wall of the mucosal capillaries and venules are common findings with venous congestion. Therefore, Misra et al. has stated that the thick gastric mucosal capillary wall is a reliable histological marker of portal hypertension than dilated gastric mucosal capillaries[65].

Patients with PHG may present with clinically significant blood loss, melena, or more commonly chronic anemia. The incidence of bleeding is more common as chronic bleeding (12%) than acute bleeding (2.5%). Bleeding related mortality reaches 12.5% [61]. Zoli et al. study has mentioned that patients with severe PHG who have severe liver dysfunction, are

liable to develop future variceal bleeding. Other studies didn't find any correlation of PHG to: (i) history of upper GI bleed; (ii) size of varices; (iii) etiology of liver cirrhosis; or (iv) liver function status. The prevalence of PHG was found higher in patients with esophagogastric varices (74 / 107; 69%) compared to those with esophageal varices alone (68 / 123; 55%; $P < 0.05$). A recent study by Stewart and Sanyal showed a stepwise increase in PHG-related bleeding risk with increasing PHG scores [66].

β- blockers (propranolol),somatostatin, octreotide , vasopressin, terlipressin and estrogen have been proposed for the treatment of PHG based on their ability to decrease gastric perfusion [67]. β- blockers are the drug of choice for prevention of GI bleeding in PHG , with the dosage titrated up to achieve a resting heart rate of approximately 60 beats per minute. In patients who do not respond to beta-blockers, a TIPS should be placed.; Portosystemic shunt surgery is another alternative in the suitable candidate[67].

Due to the lack of randomized studies , the fluctuating nature of PHG and possibly unreported failures, both TIPS and shunt surgery should be considered only as a rescue therapies for the uncommon patients who has repeated bleeding from PHG despite propranolol treatment. Liver transplantation reverses portal hypertension and therefore effectively treats PHG.

GASTRIC ANTRAL VASCULAR ECTASIA (GAVE) :

GAVE ,also known as watermelon stomach , is relatively rare . It is characterised by red patches or spots in either a diffuse or linear array in the antrum of the stomach , which can result in significant blood loss and leads to chronic iron deficiency anemia that is difficult to treat. Its etiology is unclear. Vasoactive substances may play an important role in the etiology of vascular ectasia. Neuroendocrine cells containing vasoactive intestinal peptide and 5-hydroxtryptamine have been found close to the vessels in the lamina propria of resected specimens from GAVE patients .So, these mediators may be responsible for the vasodilatation and thus the propensity to bleed .GAVE in cirrhotic patients may be explained by the shunting of blood and altered metabolism of vasoactive substances in the presence of liver disease [68] . Moreover , abnormal response to mechanical antral stress is another factor.

GAVE have several disease association as primary biliary cirrhosis (PBC) , connective tissue disease,etc…More than 70% of patients with GAVE syndrome do not have cirrhosis or portal hypertension (PBC). However, in the setting of cirrhosis, GAVE syndrome can be difficult to differentiate from PHG. Both conditions are diagnosed endoscopically as collections of discrete red spots of ectatic vessels arranged in stripes along

the antral rugal folds; however, the red spots of PHG appear in a background of mucosal mosaic appearance, but the mucosa underlying GAVE is normal. Histologically , vascular ectasia in GAVE are seen in the mucosa associated with fibrin thrombi ,fibrohylinosis and spindle cell proliferation [69]. Drugs of reported benefit include estrogen and progesterone [70]. The success of endoscopic therapies have been reported to improve lesions and decrease blood requirements , although , such treatments are not effective in patients with diffuse GAVE , such modalities include cautery by Argon Plasma Coagulator ,heater probe ,or Yag laser . Surgical treatment, including antrectomy, can cure GAVE syndrome, but in patients with cirrhosis and portal hypertension , the morbidity of surgery may be reduced by reducing portal pressure [71].

Gastroduodenal ulcers and gastroduodenal erosions are particularly frequent in cirrhotic patients, but their precise cause is unclear. However, the postulation that portal hypertensive mucosa is relatively ischemic and is liable to noxious injury may as well explain the association of such lesions.

PORTAL HYPERTENSIVE ENTEROPATHY (PHE) :

Small bowel mucosa in portal hypertension was recently assessed extensively. It is a recognized potential source of bleeding in portal hypertension. However, the frequency of its involvement is unknown. Nagral et al. has claimed that PHE is part of the spectrum of congestive gastroenteropathy and occurs at least as frequently as changes in the stomach and duodenum. In addition , its incidence doesn't correlate with the Child-Pugh score or with prior sclerotherapy [72] . Similar to PHG, several incriminating factors have been proposed including circulating hormonal vasodilators from intestinal origin such as glucagon, insufficiently cleared by the liver, as well as increased nitric oxide production. Glucagon in a dose sufficient to acutely elevate portal venous pressure aggravates noxious injury of the mucosa in rats with portal hypertension. Infusion of a portal hypotensive dose of somatostatin reverses these changes.

Misra et al has reported a significant dilatation in the mucosal vessels with thickened walls in duodenal and jejunal biopsy specimens in portal hypertensive patients compared to controls(67% and 71% vs 27% and 2% respectively)[73]. Increased mucosal mast cell infiltration suggests an inflammatory background for PHE in addition to the documented vascular changes. Other important histologic features in the portal hypertensive

patients include edema of the lamina propria, fibromuscular proliferation, a decreased villous/crypt ratio, and thickened muscularis mucosae. The clinical implication of these changes is the increased chance of occult gastrointestinal blood loss [73]. PHE is usually asymptomatic, Massive hemorrhage has only rarely been described and its management is controversial Gastrointestinal wall thickening is common on contrast-enhanced abdominal CT scans. It involves multiple segments(commonly jejunum and ascending colon).

Protein loosing enteropathy and intestinal lymphagiectasia in portal hypertension drew the attention of researchers. Stanley et al. recently suggested that the mucosal congestion may lead to protein loss in addition to blood loss , probably by dysfunction of the intestinal lymphatics ,and this could be corrected by TIPS [74].

Functionally, the spectrum of portal hypertension in the gastrointestinal tract still extends to include altered intestinal motility with delayed transit, mainly in the proximal part of the small intestine, which may predispose to bacterial overgrowth and malabsorption.

PORTAL HYPERTENSIVE COLOPATHY (PHC) :

Over the past few years, it has been observed that not only the stomach but the entire gastrointestinal tract, with its venous drainage through the portal venous system, is involved in patients with portal hypertension. Involvement of the duodenum , the small intestine , and the colon have all been described. There is continuing controversy regarding information on the involvement of the colonic mucosa in these patients. Only a few studies, however, have investigated the colon in patients with portal hypertension.

Colorectal mucosal lesions in patients with portal hypertension is termed as portal hypertensive colopathy (PHC). These are thought to be important causes of lower gastrointestinal hemorrhage, although the clinical importance of these lesions in patients with portal hypertension is not well established. The features of PHC are not well defined but include multiple vascular appearing lesions (telangiectasias, cherry red spots and angiodysplasia like lesions), colitis- like abnormalities (granularity, erythema, edema, friability), colorectal varices, or a combination of these findings [75]. The diagnostic criteria and clinical significance of this condition is confusing. This may be partially due to imprecise terminology, lack of uniform endoscopic descriptions, interobserver variability and the absence of distinctive histopathologic features.

Bini et al. and Keiichi et al. proposed a classification system for describing portal hypertensive colopathy [76,77].

Bini et al. classification :

Grade 1 - Erythema of the colonic mucosa

Grade 2 - Erythema of the colonic mucosa along with a mosaic-like appearance of the mucosa

Grade 3 - Vascular lesions of the colon, including cherry red spots, telangiectasias, or angiodysplasia-like lesions

Keiichi et al. classification :

1. Solitary vascular ectasias

2. Diffuse vascular ectasias

3. Redness

4. Blue vein

Misra et al. reported dilated tortuous mucosal capillaries with irregular thickening of wall, edema of lamina propria and mild chronic inflammatory infiltrate as the major histopathological changes seen in

colonic biopsies of patients with PHC [78]. The histological changes have no correlation with the clinical or endoscopic findings, however, the thickness of the capillary wall is higher in patients who had undergone sclerotherapy[78].

According to Bini et al. the prevalence of colonic mucosal abnormalities in patients with cirrhosis and portal hypertension is as follows, colitis like abnormalities seen in 38% of patients, vascular lesions seen in 13%, rectal varices seen in 9% and hemorrhoids seen in 46% of patients [77]. Whereas Ganguly et al. concluded in his study that colitis like abnormalities seen in 6% of patients, vascular lesions seen in 52% and rectal varices seen in 44% of patients [79]. In an another study by Misra et al. reported that colitis like abnormalities seen in 27% , vascular lesions seen in 49% , rectal varices in 40% and hemorrhoids in 36% of patients.

Misra et al. also reported that the relationship between portal hypertensive colopathy and anorectal varices is inverse. He proposed the reason for this is that the anorectal varices decompress the colonic mucosa, making portal hypertensive colopathy less common in patients with anorectal varices than in patients without these varices [78, 81].

Keiichi Ito et al. concluded in his study that the prevalence of portal hypertensive colopathy increases as the child pugh class worsens in patients with cirrhosis. Whereas Bresci et al. described in his study that the type and prevalence of colonic lesions in cirrhotic patients are not associated with the either etiology or severity of cirrhosis. [82]

Keiichi Ito et al. also described an interesting observation from his study that the prevalence of portal hypertensive colopathy increases with decreases in platelet count [82]. This observation was not seen in any of the other published series.

It has been reported by many of the authors [77,83,84,85] that sclerotherapy or band ligation of esophageal varices may promote the development of colonic varices and mucosal lesions; however, Misra et.al. reported that sclerotherapy or band ligation for esophageal varices did not have any significant effect on the prevalence of mucosal abnormalities in the colon. Later Bresci et al. also concluded in his study that the prevalence of colonoic mucosal abnormalities does not increase with prior endoscopic treatment of esophageal varices [76].

In a study by El Kady et al. concluded that the severity or grading of esophageal varices does not correlate with prevalence of portal hypertensive

colopthy [86]. Similarly Misra et al and Bini et al found no clear relationship between large esophageal varices or severity of portal hypertensive gastropathy and portal hypertensive colopathy [77,75].

Misra et al. described in his study that the features of portal hypertensive colopathy is more commonly seen in the left side of the colon [75]. Whereas Kozarek et al. [87] noted it to be more common in the right side and Bini et al. noted that the pancolonic involvement is more common [77].

Sarin et al. concluded that the frequency of portal hypertensive colopathy is nearly equal in cirrhosis, Non cirrhotic portal hypertension and Extrahepatic portal venous obstruction whereas the rectal varices were more often seen in EHPVO than NCPF and cirrhosis and also it was found to be larger in EHPVO than NCPF and cirrhosis [79].

Rectal EUS is used recently for evaluation of the anorectal region in portal hypertension . Dhiman et al . studied changes in the venous system of the rectum using endoscopy and EUS in 60 patients with portal hypertension (cirrhotic 41, noncirrhotic 19) and 10 controls [88]. Prevalence of rectal varices was 43.3% on endoscopy and 75% on EUS ($p < 0.0005$). Congestive rectopathy was found in 38.3% of patients. Multiple small dilated vessels in the submucosa were seen in 23.3% of patients on rectal

EUS. The development of these vascular changes was significantly influenced by sclerotherapy, but not by higher grade of esophageal varices, the etiology of portal hypertension, or severity of liver disease.

The mucosal changes in PHC may require pharmacological, directed endoscopic, or portal decompressive therapy , so octreotide may find a place in its treatment. TIPS has recently been suggested to be useful in the therapy of bleeding from parastomal , vascular ectasia like lesions or anorectal varices in patients unresponsive to conservative therapy [83,84].

Most of the prospective studies and published reports which investigated the colonic mucosal changes in patients with liver cirrhosis and portal hypertension are often based on patients with overt lower gastrointestinal symptoms. Very few studies have investigated in asymptomatic patients. Therefore in our study we have evaluated the colonic mucosal abnormalities in liver cirrhosis and portal hypertension patients without any lower gastrointestinal symptoms as a screening and assessed the clinical significance of such lesions and its relationship with severity of liver failure, grading of esophageal varices and the effect of endoscopic variceal ligation.

AIM OF THE STUDY

1. To find out the prevalence of colonic mucosal abnormalities in patients with cirrhosis and portal hypertension.
2. To assess the relationship between colonic mucosal abnormalities and the severity of liver disease.
3. To assess the relationship between colonic mucosal abnormalities and the grading of esophageal varices.
4. To investigate the effect of endoscopic variceal ligation of the esophageal varices on the colonic mucosal changes.

MATERIALS AND METHODS

Place of study : Department of Digestive Health and Diseases, Government Peripheral hospital, Anna nagar, Chennai.

Type of study : Prospective study.

Period of study : December 2008 to December 2010.

Ethical committee : Approval obtained.

Consent : Informed consent obtained from all participants

Selection of patients :

Inclusion criteria :

- Age between 18 and 65 years
- **Group 1 -** 30 consecutive newly diagnosed patients with cirrhosis and Portal hypertension not exposed to medical and endoscopic treatment.
- **Group 2 -** 30 patients with cirrhosis and portal hypertension Who underwent atleast 1or more sessions of

endoscopic variceal Ligation for variceal obliteration.

Exclusion criteria :

- Previous surgical intervention for portal hypertension
- Patient on primary pharmacological prophylaxis for variceal bleeding
- Coexisting cardiac disease, patients on beta blockers
- Patients with colitis
- Patients with chronic kidney disease
- Hepatocellular carcinoma detected by ultrasound
- Advanced comorbidity for endoscopy
- Patients operated for haemorrhoids
- Personal history of malignancy
- Patients with primary sclerosing cholangitis
- Patients with active G I bleed

Clinical evaluation:

All patients underwent a detailed clinical evaluation at entry. Detailed history and physical characteristics including age, gender, signs of

liver failure (spider angioma, palmar erythema etc.), hepatomegaly, splenomegaly, ascites and abdominal vein collaterals were recorded. All patients selected for the study underwent the following investigations;

Blood and Stool tests:

Hematological and biochemical workup included measurement of hemoglobin, total leukocyte count, platelet count, prothrombin time, and serum concentrations of bilirubin (total and conjugated), protein, albumin, alanine aminotransferase and aspartate aminotransferase. For each patient, severity of liver failure was calculated using Child-Pugh score.[9] All patients were tested for HBsAg and antibodies to hepatitis C virus using enzyme immunoassays to determine the cause of liver cirrhosis. Tests for other causes of cirrhosis (serum ceruloplasmin and slit lamp examination for Wilson's disease, tests for autoantibodies for autoimmune liver disease, iron studies for hemochromatosis) were carried out only if there was a suggestive clinical clue. In patients with ascites, ascitic fluid was tapped under aseptic precautions and ascitic fluid albumin and serum-ascites albumin gradients were measured to document high SAAG ascites. All patients stool was examined for ova, cyst and occult blood.

Ultrasound Doppler:

All patients underwent ultrasonography after over night fast and the following details were recorded: maximum vertical span of the liver; nodularity of liver surface; SOL in liver; spleen size; diameter of the portal and splenic veins; presence of portal-systemic collaterals; and presence of ascites.

Endoscopic evaluation:

All patients underwent upper gastrointestinal endoscopy for assessment of esophageal and gastric varices using video gastroscope (PENTAX) with in 2-3 days of admission. If esophageal varices were present, their size was graded as I-IV, using the Paquet grading system[94]. Presence of gastric varices, portal hypertensive gastropathy, duodenopathy and were recorded in all the patients. Gastric varices were classified according to Sarin classification.[93]

Full length colonoscopic examination of the lower gastrointestinal tract was performed (PENTAX Video Colonoscope) in each patient after adequate bowel preparation using polyethylene glycol electrolyte solution completed atleast 6 hours prior to the study. During colonoscopy, a careful search was made for hemorrhoids, anorectal varices, colonic varices and

mucosal lesions of portal hypertensive colopathy. Briefly, hemorrhoids were defined as large venous structures at or just proximal to the anus. Anorectal varices were defined as bluish or gray, distended, tortuous or saccular veins seen well above the anal margin, extending into the rectum. If such a lesion was seen above the rectum it was termed a colonic varix. Portal hypertensive colopathv was defined as diffuse hyperemia and edema resembling chronic colitis, lesions such as spider angiomas, patchy localized hyperemic lesions, or severe hyperemia with an acute colitis-like picture with spontaneous bleeding from the colonic mucosa[78].

Endoscopic Variceal Ligation was performed using Variclear Band Ligator by Wilson Cook Medicals. Six bands were placed in one session. EVL was performed every fortnightly. All the patients in group 2 underwent atleast two sessions of EVL. None of the patients received beta blockers during EVL. Colonoscopy was performed six weeks after the last EVL session.

Diagnosis of cirrhosis was based on clinical, biochemical, and ultrasonographic findings. All patients were followed up for a period of atleast six months to one year.

STATISTICAL ANALYSIS :

Statistical analyses were carried out to compare continuous variables using Student's t test. Chi−squared analysis was used to evaluate categorical variables. A two−tailed P value of <0.05 was considered statistically significant. All analyses were performed using SPSS 16.0 (SPSS Inc. Chicago, IL).

RESULTS

The total number of patients included in this study was 30 in group 1 and 30 in group 2.

TABLE 1 : Age Distribution

Age	Group 1	Group 2
Range	22 – 65	32 – 65
Mean	47.57	47.53
Standard deviation	11.43	11.56

The mean age of the patients in group 1 was 47.57 (range 22 – 65 yr) and in group 2 was 47.53 (range 32 – 65 yr)

TABLE 2 : Sex Distribution

Sex	Group 1	Group 2
Male	24 (80%)	21 (70%)
Female	6 (20%)	9 (30%)
Total	30	30

P value = 0.371

Out of 30 patients in group 1, 24 were males and 6 were females whereas in group 2, 21 were males and 9 were females. There was no statistically significant difference between the two groups.

TABLE 3 : Esophageal Variceal Grading in Group 1

Esophageal variceal grade	Group 1
Grade 1	0
Grade 2	13 (43.3%)
Grade 3	15 (50%)
Grade 4	2 (6.7%)
Total	30

Out of 30 patients in group 1, 13 patients had grade 2 varices, 15 had grade 3 varices and 2 patients had grade 4 varices.

TABLE 4 : CTP Class Distribution in Group 1

CTP	Group 1	Group 2
A	6 (20%)	6 (20%)
B	14 (46.7%)	11 (36.7%)
C	10 (33.3%)	13 (43.3%)
Total	30	30

Out of 30 patients in group 1, 6 belonged to CTP class A, 14 belonged to CTP class B and 10 belonged to CTP class C.

TABLE 5 : Etiology Distribution

ETIOLOGY	Group 1	Group 2
Ethanol	20 (66.7%)	17 (61.7%)
HBV	3 (10%)	5 (16.7%)
HCV	1 (3.3%)	0
Auto immune	2 (6.7%)	3 (10%)
Wilson	1 (3.3%)	0
Cryptogenic	3 (10%)	5 (16.7%)
Total	30	30

P value = 0.632

Majority of patients in both the groups, the etiology for chronic liver disease was due to ethanol (66.7% in group 1 and 61.7% in group 2).

TABLE 6 : Hemorrhoids

Hemorrhoids	Group 1	Group 2
Present	6 (20%)	8 (26.7%)
Absent	24 (80%)	22 (73.3%)
Total	30	30

P value = 0.542

In group 1, 6 out of 30 patients had hemorrhoids (20%) whereas in group 2, 8 out of 30 patients had hemorrhoids (26.7%). There was no statistically significant difference between the two groups. Hence prior variceal obliteration by endoscopic variceal banding did not increase the prevalence of hemorrhoids in our study.

TABLE 7 : Rectal Varix

Rectal varix	Group 1	Group 2
Present	3 (10%)	3 (10%)
Absent	27 (90%)	27 (90%)
Total	30	30

P value = 1.00

In both group 1 and 2, 3 patients had rectal varix (10%). There was no statistically significant difference between the two groups. Therefore, endoscopic variceal banding did not increase the development of rectal varix in our study.

TABLE 8 : Portal Hypertensive Colopathy

PHC	Group 1	Group 2
Present	15 (50%)	17 (56.7%)
Absent	15 (50%)	13 (43.3%)
Total	30	30

P value = 0.605

In group 1, 15 out of 30 patients showed colonoscopic features of portal hypertensive colopathy (50%) whereas in group 2, 17 out of 30 patients had features of portal hypertensive colopathy (56.7%) which was not statistically significant.

Therefore, prior variceal obliteration by endoscopic variceal ligation did not increase the prevalence of portal hypertensive colopathy in our study.

TABLE 9 : Correlation Between Esophageal Variceal Grading and PHC in Group 1

PHC	Esophageal Variceal Grading				Total
	Grade 1	Grade 2	Grade 3	Grade 4	
Present	0	2 (13.3%)	11 (73.3%)	2 (100%)	15
Absent	0	11(73.3%)	4 (26.7%)	0	15
Total	0	13	15	2	30

P value = 0.03

In group 1, 2 out of 13 patients with grade 2 varices, 11 out of 15 patients with grade 3 varices and 2 out of 2 patients with grade 4 varices had portal hypertensive colopathy.

Therefore, the chances of patient having portal hypertensive colopathy increases as the increase in esophageal variceal grading.

TABLE 10 : Correlation Between PHC and CTP Class in Group 1

PHC	CTP class			Total
	A	B	C	
Present	1 (16.6%)	6 (42.8%)	8 (80.9%)	15
Absent	5(83.4%)	8(57.2%)	2(19.1%)	15
Total	6	14	10	30

P value = 0.043

In group 1, 1 out of 6 patients in CTP class A (16.6%), 6 out of 14 in class B (42.8%) and 8 out 10 in class C (80.9%) showed showed features of portal hypertensive colopathy in colonoscopy which was statistically significant.

Therefore, the prevalence of portal hypertensive colpathy increases as the CTP class worsens.

TABLE 11 : PHC Site Distribution in Group 1

PHC	Group 1	Group 2
Left colon	8 (53.3%)	10 (58.8%)
Right colon	3 (20%)	2 (11.7%)
Diffuse	4 (26.7%)	5 (29.4%)
Total	15	17

P value = 0.532

Majority of patients in both the groups (53.3% in group 1 and 58.8% in group 2) showed predominant left sided colonic I involvement. There was no statistically significant difference between the two groups.

TABLE 12 : Specific Lesions in PHC

Type of lesion	Group 1	Group 2
Erythema alone	6 (40%)	8 (47%)
Colitis like	5 (33.3%)	4 (23.5%)
Vascular lesions	4 (26.6%)	5 (29.5%)
Total	15	17

P value = 0.542

Majority of patients in both the groups showed erythema alone (40%) in group 1 and 47% in group 2). There was no statistically significant difference between the two groups.

DISCUSSION

Prevalence of portal hypertensive colopathy :

In our study, the prevalence of portal hypertensive colopathy (PHC) in group 1 (treatment naïve) was 50% and in group 2 (post EVL) was 56.7% which is more or less similar to the previously published studies.

In a prospective study done by Bresci et al. [76] , 85 patients with cirrhosis and portal hypertension with no other significant disease underwent colonoscopy to evaluate the prevalence of portal hypertensive colopathy, and concluded that the prevalence of portal hypertensive colopathy in patients not exposed to endoscopic treatment was 54% and in patients exposed to endoscopic treatment like Enodoscopic Sclerotherapy (EST) or Endoscopic Variceal Ligation (EVL) for variceal bleed was 53% which was not statistically significant.

Similarly, Misra et al.[78] did a prospective study in 60 patients with cirrhosis and portal hypertension before and 6 weeks after EVL and obliteration of varices for variceal bleed and they concluded that the prevalence of portal hypertensive colopathy was 57% before EVL and 57%

after EVL and there was no statistically significant difference between the groups.

In other prospective studies by Ghosal et al.[89] and Kady et al.[86] also showed in their studies that there was no relation between the occurrence of PHC and prior variceal obliteration by EVL.

To the best of our knowledge, most of the previously published series concluded that there was no relation between the prevalence of PHC and endoscopic variceal obliteration with the exception of only one retrospective study by Bini et al.[77] in 437 patients with cirrhosis and portal hypertension which showed that the prevalence of PHC increases with prior EVL for variceal obliteration.

Comparison of prevalence of PHC in various published studies before EVL/ EST

Study	No. of patients	Prevalence of PHC
Bini et al.[77]	437	49%
Misra et al.[78]	60	57%
Keiichi et al.[82]	47	66%
N.EL.Kady et al.[86]	40	72.5%

Bresci et al.[76]	85	54%
Present study	**30**	**50%**

Prevalence of Rectal Varix :

In our study, the prevalence of rectal varix in both group 1 (treatment naïve) and group 2 (post EVL) was 10%. There was no statistically significant difference observed between the two groups.

Misra et al. [78]did a prospective study in 60 patients with cirrhosis and portal hypertension before and after EVL for variceal bleed and they concluded that the prevalence of rectal varix was 40% in both the situation which was not statistically significant.

In a prospective study conducted by Tam et al.[84] in 75 patients with cirrhosis and portal hypertension (more than 80% were HBV or HCV positive), they concluded that the prevalence of rectal varix was 16%.

In an another prospective study by Ghosal et al.[89] 41 patients with cirrhosis and portal hypertension were subjected to colonoscopic examination of the lower gastrointestinal tract and concluded that the prevalence of rectal varix in these patients was 36%. They also concluded that the presence of rectal varix rather than portal hypertensive colopathy

correlates with the occurrence of hematochzia and none of the parameters like CTP class, esophageal variceal eradication by EST with or without EVL predicted the occurrence of rectal varices as well as portal hypertensive colopathy.

Surprisingly, in an another prospective study done by Goenka et al.[90] they concluded that the frequency of rectal varix in 75 patients with cirrhosis and portal hypertension was as high as 89%.

Comparison of prevalence of rectal varix in various published studies

Study	No. of patients	Prevalence of rectal varix
Tam et al.[84]	75	16%
Ghosal et al.[89]	41	36%
Kozarek et al.[87]	20	25%
Goenka et al.[90]	75	89%
Ganguly et al.[79]	50	44%
Misra et al.[78]	60	40%
Bresci et al.[76]	85	34%

Present study	**30**	**10%**

Prevalence of hemorrhoids :

In our study, the prevalence of hemorrhoids in group 1 (treatment naïve) and group 2 (post EVL) was 20% and 26.7% respectively. There was no statistical difference observed between the two groups. The prevalence of hemorrhoids in adult general population is 10% to 25%.[95]

In a prospective study done by Bresci et al.[76] , 85 patients with cirrhosis and portal hypertension with no other significant disease underwent colonoscopy to evaluate the prevalence of hemorrhoids, and concluded that the prevalence of hemorrhoids was surprisingly as high as 70%.

Misra et al did a prospective study in 60 patients with cirrhosis and portal hypertension before and 6 weeks after EVL therapy for variceal obliteration and reported that the prevalence of hemorrhoids was 37% before EVL and 37% after EVL therapy. They finally concluded that EVL had no significant effect on the frequency of hemorrhoids[78].

Comparison of prevalence of hemorrhoids in various published series

Study Group	No. of patients	Prevalence of hemorrhoids
Bresci et al.[76]	85	70%
Misra et al.[78]	60	37%
Goenka et al.[90]	75	41%
Ghosal et al.[89]	41	22%
Present study	**30**	**20%**

In contrast to the other published series, the lower frequency of rectal varices and hemorrhoids in our study might be explained by differences in the patient populations studied, interobserevr variability among endoscopists or differences in indications of colonoscopy. Most if not all the above mentioned studies have done colonoscopy in patients with overt lower gastrointestinal symptoms whereas in our study, colonoscopy

was done as a screening test in patients with cirrhosis and portal hypertension without overt lower gastrointestinal blood loss.

Comparison of colonic mucosal abnormalities between the two groups

Study group	Findings	Group 1 (treatment naive)	Group 2 (post EVL)	P value
Misra et al.[78]	**PHC**	57%	57%	**Not significant**
Bresci etal.[76]		54%	53%	
Present study		50%	56.7%	
Misra et al.[78]	**Rectal varix**	40%	40%	
Bresci et al.[76]		34%	28%	
Present study		10%	10%	
Misra et al.[78]	**Hemorrhoids**	37%	37%	
Present study		20%	26.7%	

It appears that following EVL, the colonic mucosa and anorectal varices escape the effects of variceal obliteration since they are furthest from the esophageal varices and the brunt of the congestion is borne by the

adjacent gastric mucosa resulting in increase in the occurrence of portal hypertensive gastropathy as documented by previously published studies.

None of the patients in both the groups developed overt lower G I bleeding during the follow up.

Correlation of PHC and CTP class :

In our study, 16.6% of patients in CTP class A, 42.8% of patients in CTP class B and 80% of patients in CTP class C had Portal Hypertensive Colopathy.

In contrast to previously published studies by Kozarek et al[87], Ganguly et al[79], and Bresci et al[76], our study demonstrated that the prevalence of PHC increased with worsening of CTP class which was statistically significant with a p value of 0.043.

Similar to our study, Keiichi et al, Kady et al[86] and Bini et al[77] showed in their studies that the prevalence of PHC increases with worsening of liver failure as indicated by CTP class.

Correlation of PHC and Esophageal Variceal Grading :

In our study, 13.3% of patients with grade 2 esophageal varices, 73.3% of patients with grade 3 varices and 100% of patients with grade 4

varices had PHC. Therefore, our study demonstrated that the chances developing PHC increases with increasing size of the esophageal varices which was statistically significant with a p value of 0.03.

Almost all the previously published studies (N.EL.Kady et al[86], Keiichi et al[82] and Ghosal et al.[89])which assessed the relationship between PHC and esophageal variceal grading showed that there was no relation between the occurrence of PHC and esophageal variceal grading with the exception of only one prospective study by Misra et al. which showed that the incidence of PHC was higher in patients with larger esophageal varices.

PHC and site predilection :

In our study, more than 50% of the patients in both the groups showed predominant left sided colonic involvement which is similar to the study published by Misra et al[78]. Whereas in a retrospective study by Bini et al.[77] showed 74% of the patients showed diffuse colonic involvement.

In an another prospective study by Kozarek et al.[87] right colonic involvement was more common than the left colon.

Colonic varices :

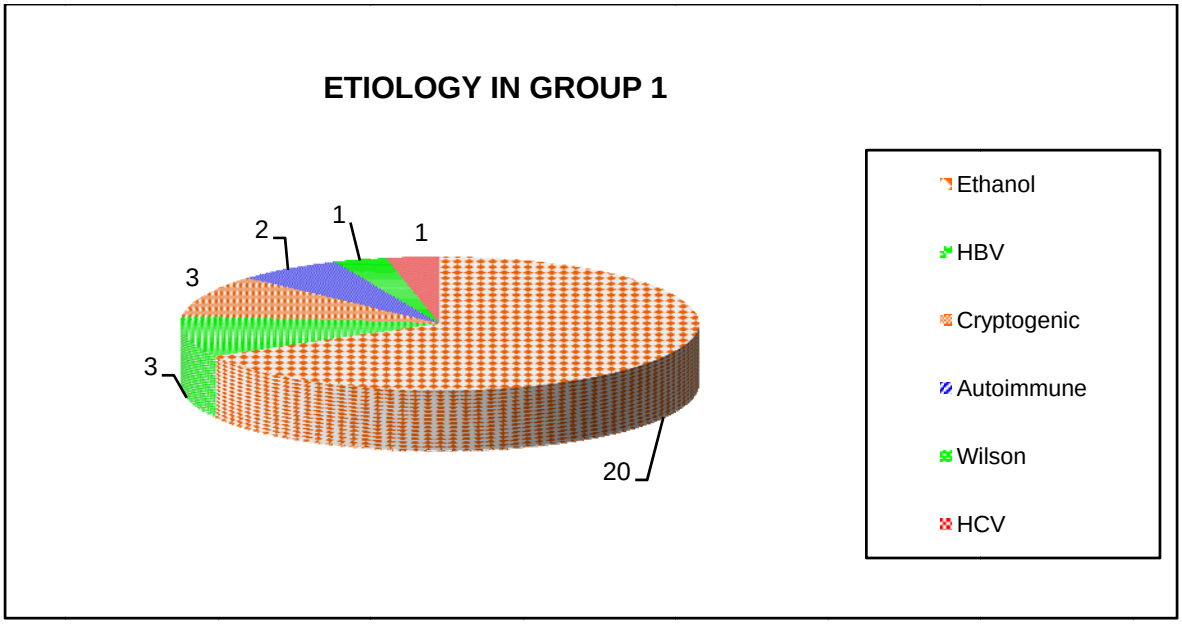
In our study, none of the patients in both the groups had colonic varices. Similar to our study, Misra et al.[78] and Naveau et al[91] also noted that none of the patients had colonic varices in their study cohort of 50 patients and 100 patients respectively. In an another study by Ganguly et al.[79] colonic varices were noted in only one out of 50 patients studied.

CONCLUSION

1. The prevalence of portal hypertensive colopathy, rectal varix and hemorrhoids in patients with cirrhosis and portal hypertension was 50%, 10% and 20% respectively.

2. The prevalence of portal hypertensive colopathy in patients with cirrhosis and portal hypertension increases with worsening of Child Pugh Turcotte score and increasing grading of esophageal varices.

3. Esophageal variceal obliteration by endoscopic variceal ligation did not influence the occurrence of any of the colonic mucosal abnormalities in patients with cirrhosis and portal hypertension.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2
1
3
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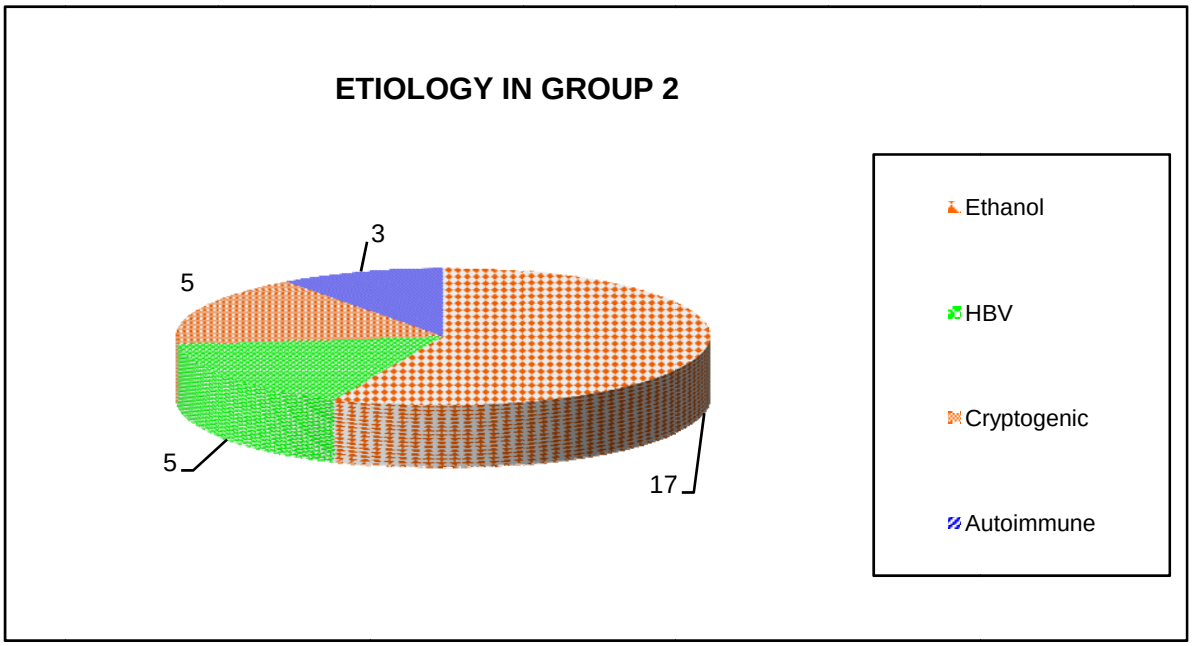
HBV
Cryptogenic
Autoimmune
Wilson
HCV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5
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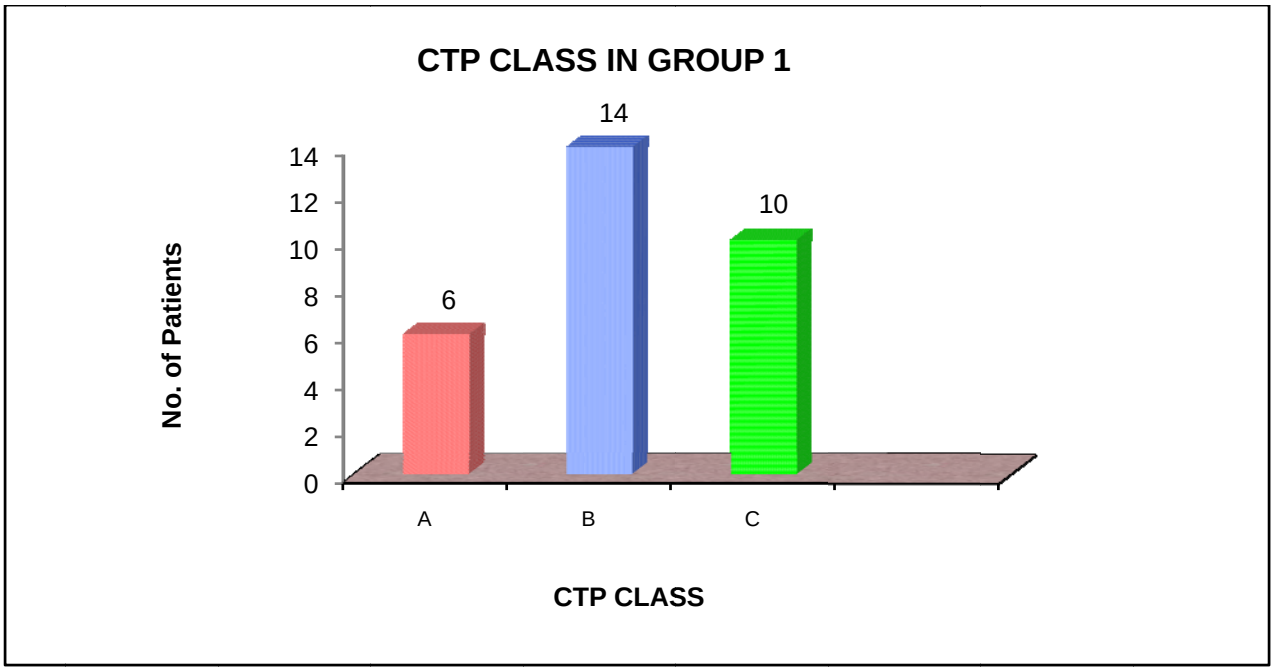
HBV
Cryptogenic
Autoimmune


CTP CLASS IN GROUP 1
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6
14
10
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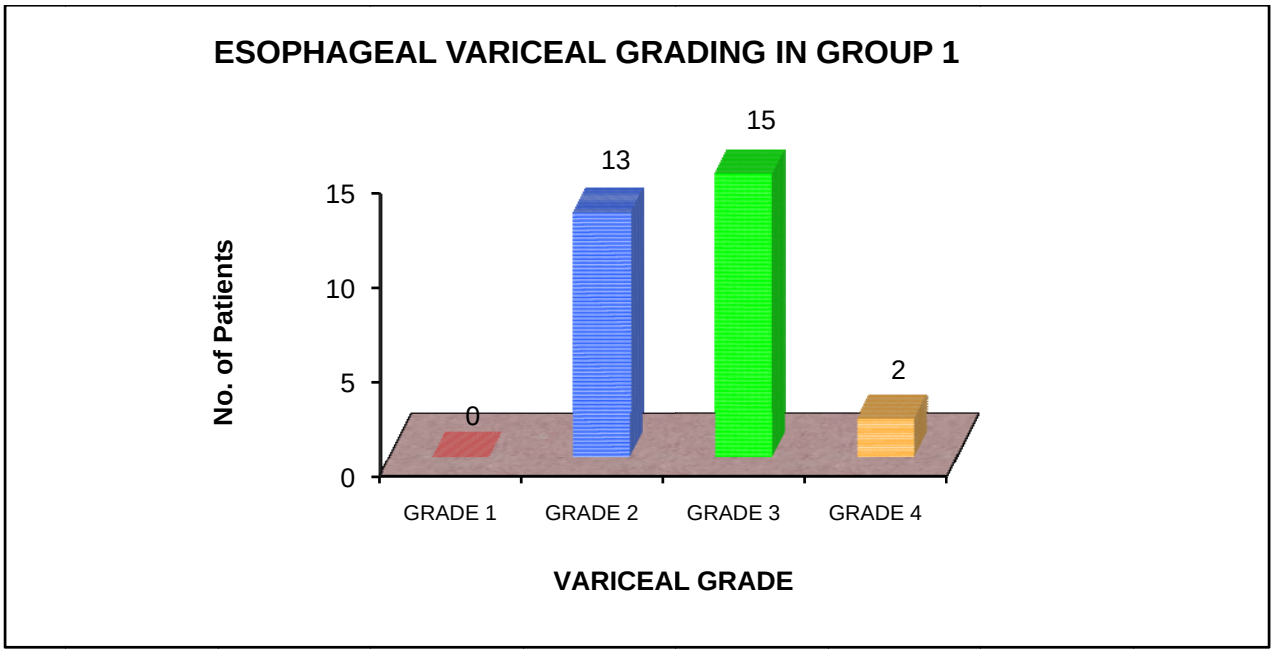
B
C
CTP CLASS


ESOPHAGEAL VARICEAL GRADING IN GROUP 1
No. of Patients
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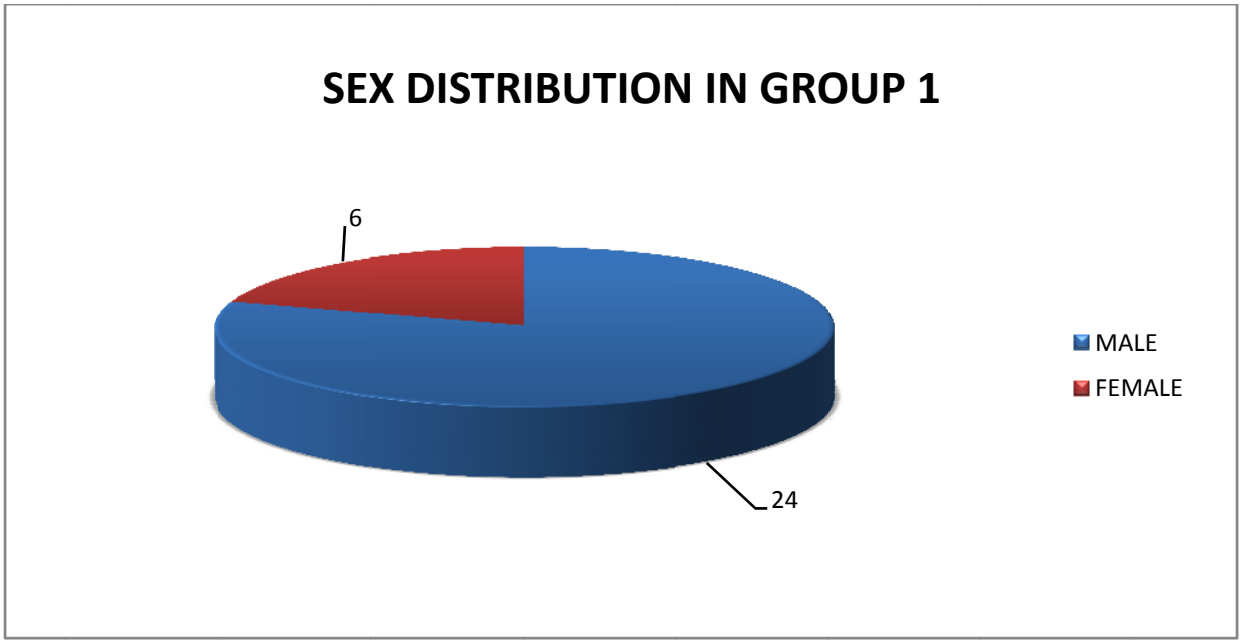
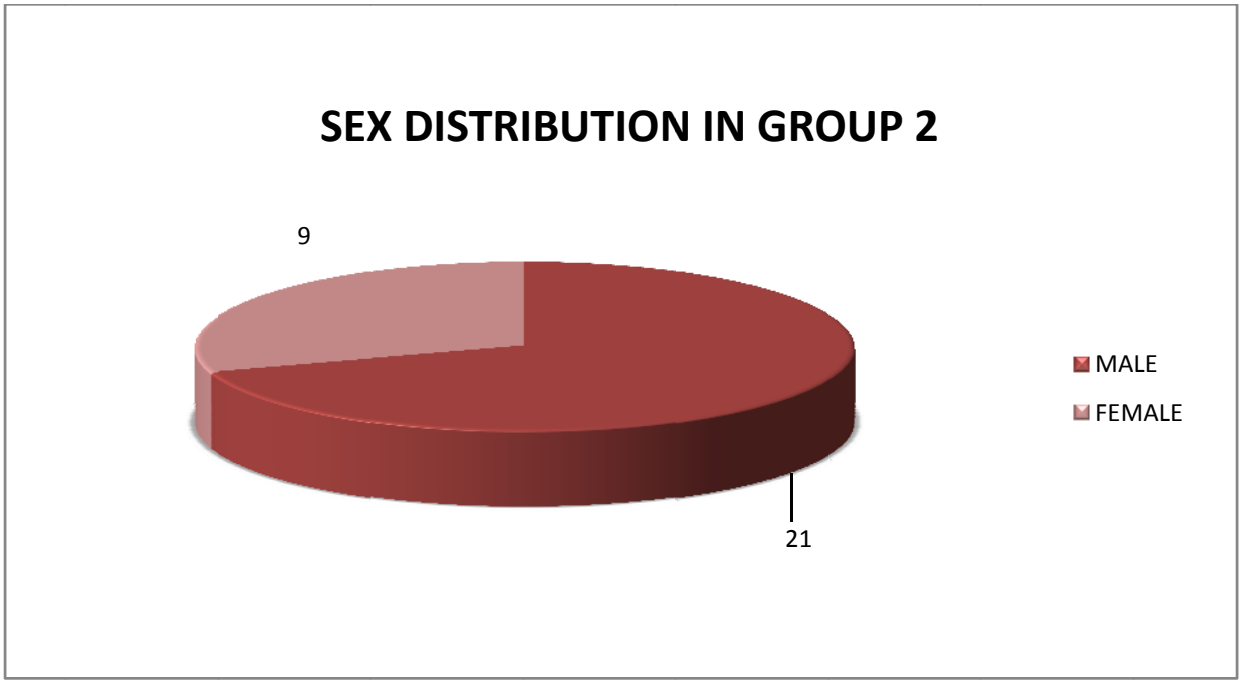
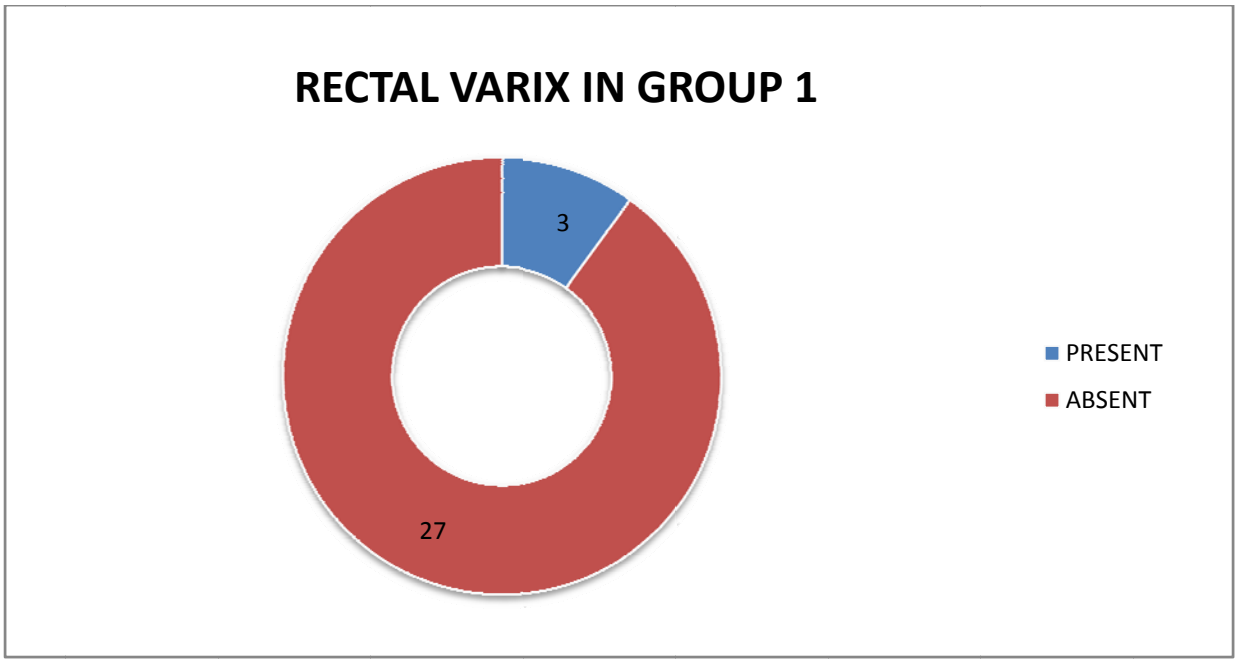
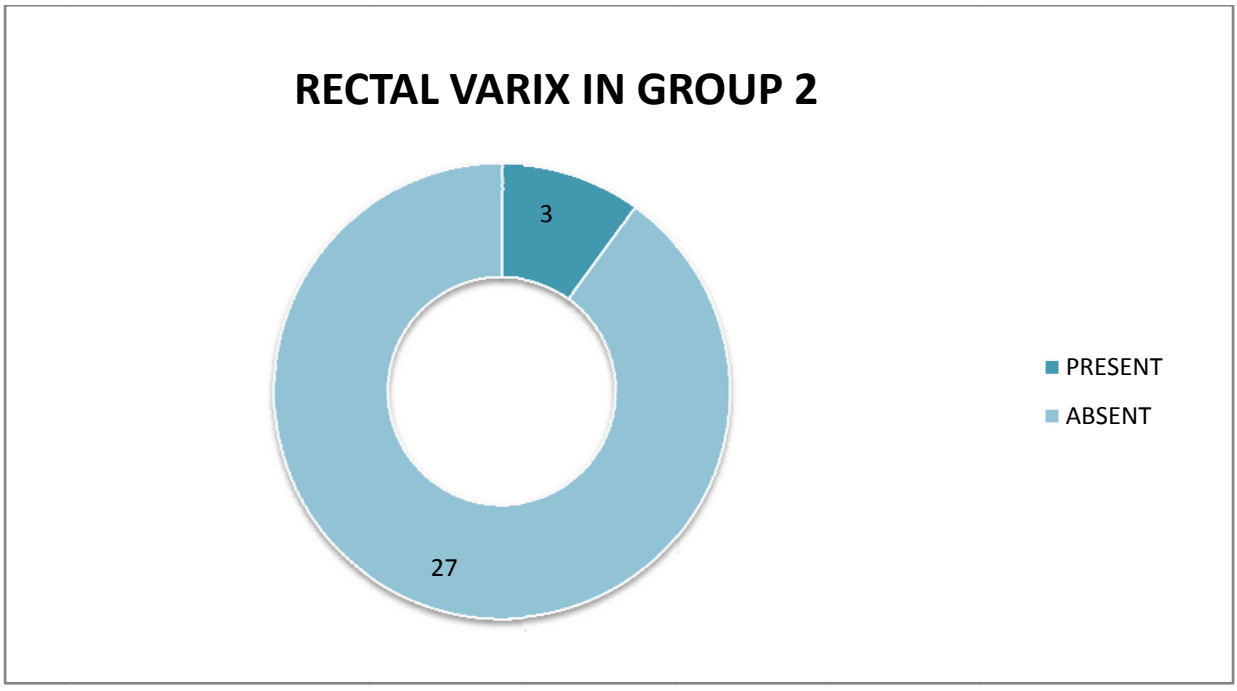
0
13
15
2
GRADE 1
GRADE 2
GRADE 3
GRADE 4
VARICEAL GRADE

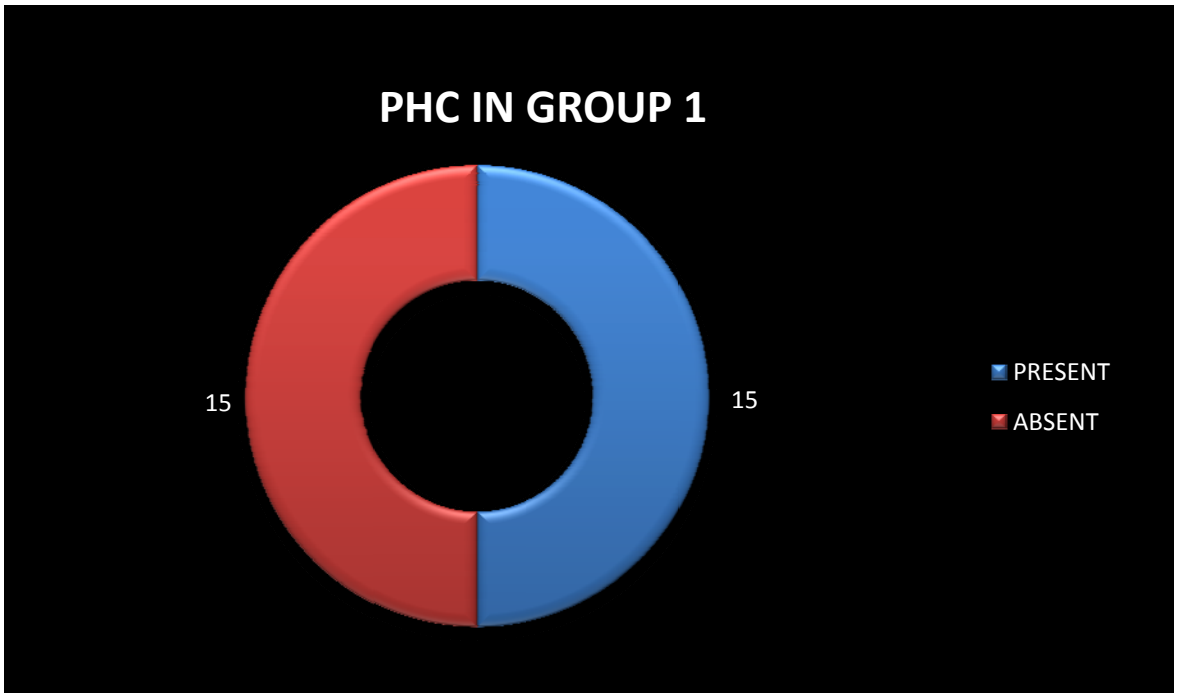
S

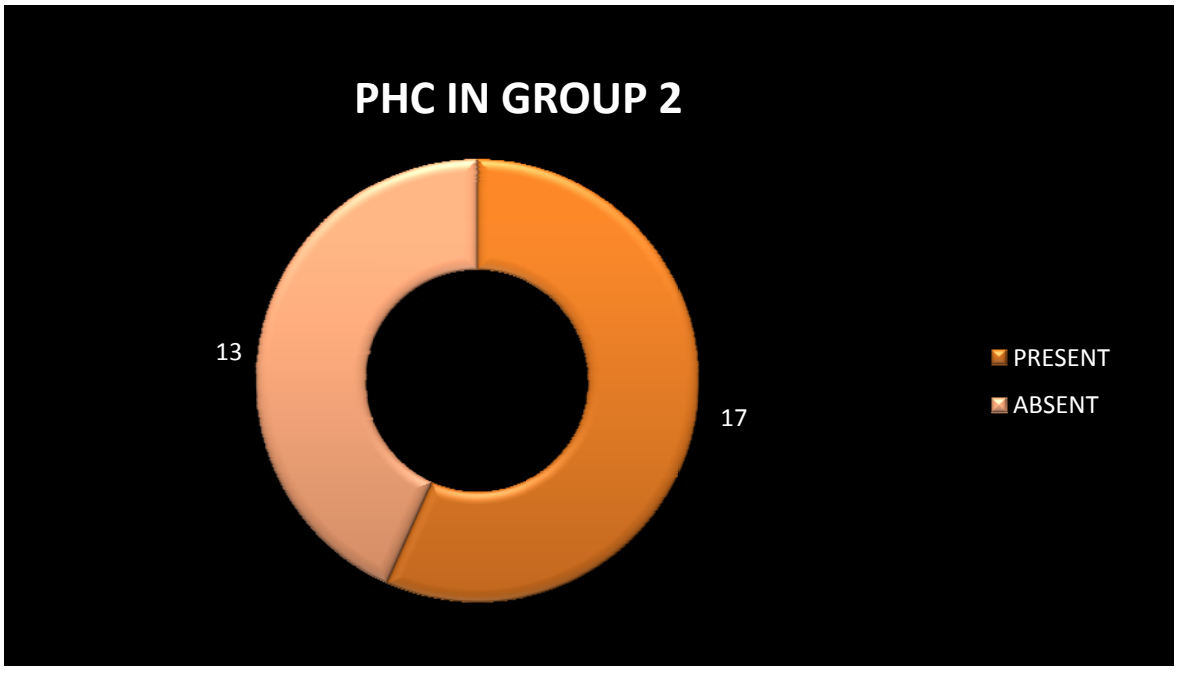

SEX DISTRIBUTION IN GROUP 1
6
24
MALE
FEMALE


SEX DISTRIBUTION IN GROUP 2
9
21
MALE
FEMALE


RECTAL VARIX IN GROUP 1
3
27
PRESENT
ABSENT


RECTAL VARIX IN GROUP 2
3
27
PRESENT
ABSENT


PHC IN GROUP 1
15
15
PRESENT
ABSENT


PHC IN GROUP 2
13
17
PRESENT
ABSENT

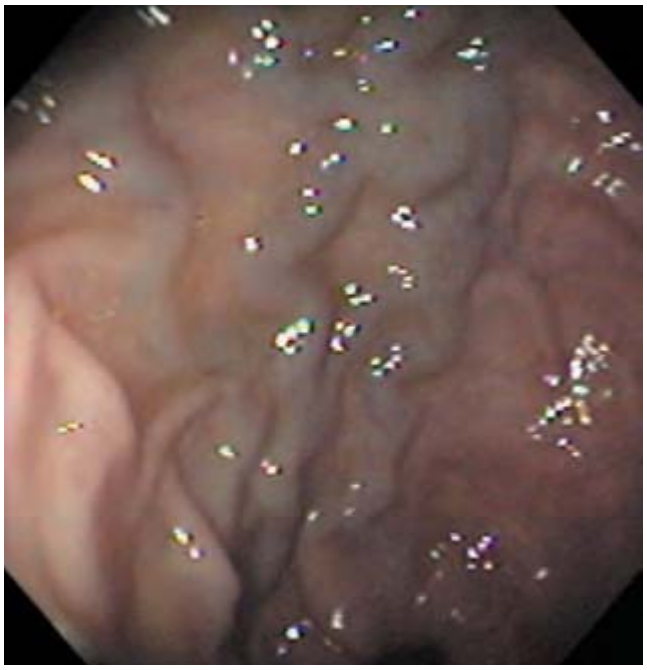


Fig 1 : Rectal Varices

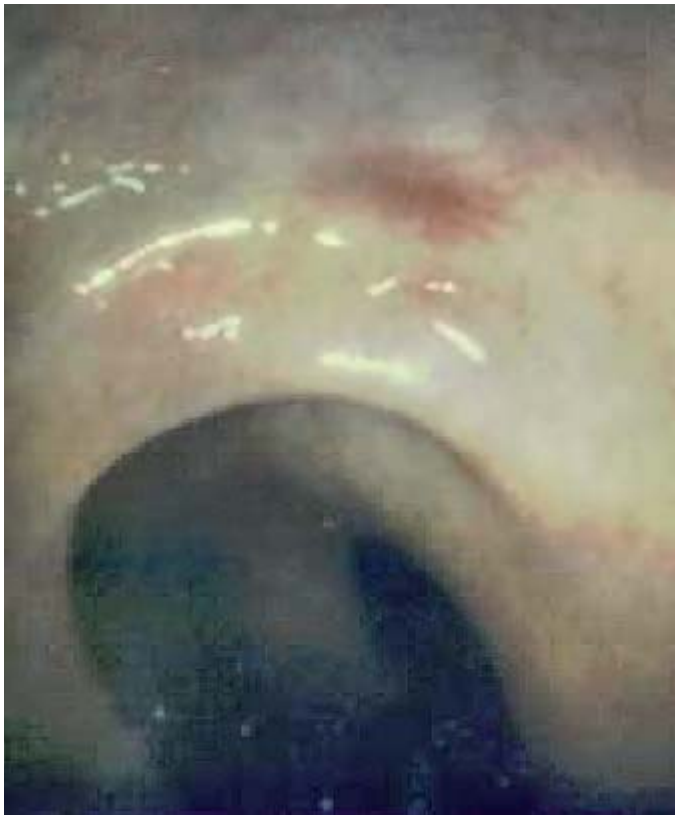


Fig 2 : Angiodysplasia like lesion

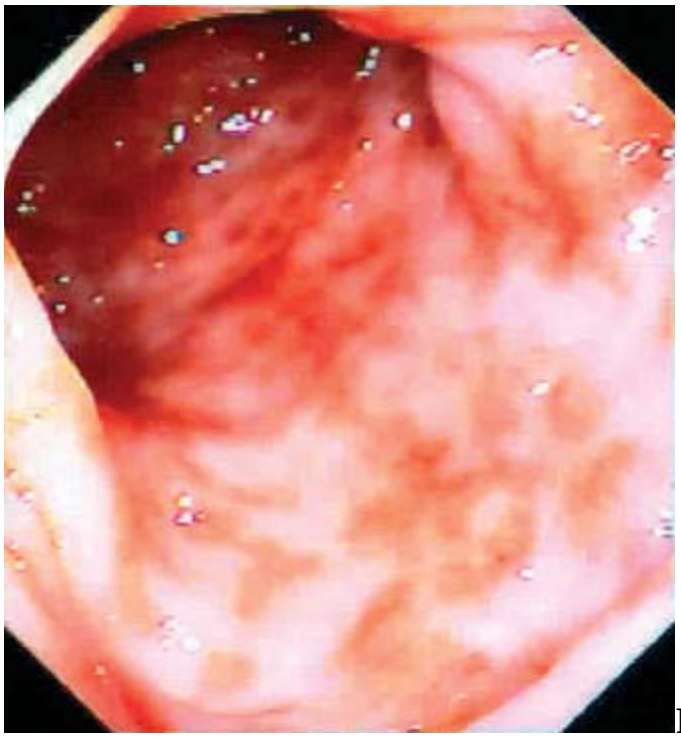


Fig 3 : Patchy erythema

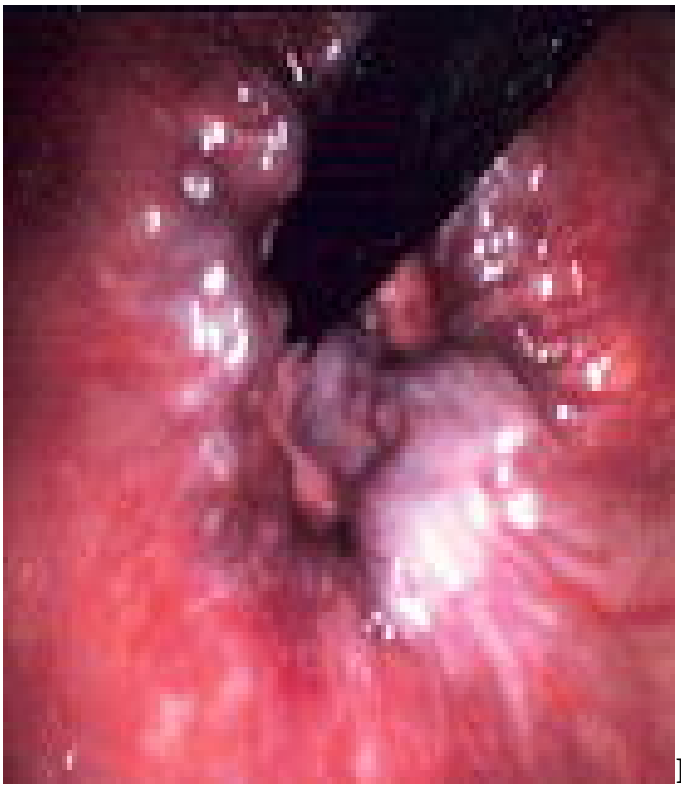


Fig 4 : Hemorrhoids

S.NO	AGE	SEX	CTP	OV.GR	COL	LENGTH	G.V	PHG	COLONOSCOPY			ETIOLOGY
									HEMORR	R.VARIX	PHC	
1	44	1	1	3	2	12	0	1	1	0	0	ETHANOL
2	40	1	3	3	4	6	0	1	0	0	1	ETHANOL
3	39	1	2	3	2	15	0	1	0	0	1	ETHANOL
4	65	2	1	3	4	10	0	0	0	1	0	CRYPT
5	46	1	3	3	2	15	0	0	0	0	1	ETHANOL
6	44	1	3	3	3	8	0	1	0	0	0	ETHANOL
7	64	2	3	4	4	15	0	1	0	0	1	CRYPT
8	65	1	1	3	3	8	0	1	0	0	1	ETHANOL
9	40	1	2	3	3	10	0	0	0	0	1	ETHANOL
10	65	1	3	3	2	6	0	0	0	0	1	HCV
11	38	2	1	3	4	12	1	1	0	0	0	AIH
12	65	1	2	3	4	15	0	1	0	0	1	ETHANOL
13	45	1	1	2	2	8	1	0	0	0	0	ETHANOL
14	52	1	3	2	2	10	0	1	0	0	1	HBV
15	52	1	2	3	2	8	0	0	0	0	1	ETHANOL
16	30	1	1	2	2	6	0	1	0	0	0	ETHANOL
17	54	1	2	3	2	5	0	0	0	0	1	ETHANOL
18	44	1	3	2	3	6	0	0	0	1	0	ETHANOL
19	43	1	2	2	3	8	0	0	0	0	1	HBV
20	48	1	3	2	2	5	1	0	0	1	0	HBV
21	30	1	2	2	2	6	0	0	1	0	0	ETHANOL
22	60	1	3	3	2	8	0	0	1	0	1	ETHANOL
23	49	1	2	2	2	10	1	0	0	0	0	ETHANOL
24	22	2	2	2	2	6	0	0	0	0	0	WILSONS
25	38	1	2	3	2	8	0	0	0	0	1	ETHANOL
26	45	1	2	2	2	8	0	0	1	0	0	ETHANOL
27	49	1	2	2	3	8	1	0	0	0	0	ETHANOL
28	65	2	3	4	2	8	0	0	0	0	1	CRYPT
29	42	1	2	2	2	6	0	0	1	0	0	ETHANOL
30	44	2	2	2	3	6	0	0	1	0	0	AIH

Proforma Case No :

Name : DDHD No :

Age : IP No :

Sex : VOGD No :

Occupation : Address :

Symptoms & Duration :

Abdominal distention	Leg swelling	Jaundice
Melena / hemetemesis	Vomiting	Bleeding tendencies
Altered sensorium	LOW	LOA
Lethargy	Decreased urine output	

Past history :

Similar episodes	Jaundice	Surgery
Blood transfusion	Tattooing	Drug abuse
Native drugs	P.TB	DM
SHT	IHD/BA	

Personal history :

Marital status :	Siblings	Children
Smoking	Quantity	Duration
Alcohol	Quantity	Duration

High risk behavior

IV Drug abuse Diet and Medications

Menstrual history : Obstetric history :

Examination :

Ht :	Wt :	BMI :
Pallor	Icterus	Pedal edema
Clubbing	Cyanosis	LN
Spider naevi	Scratch marks	Palmar erythema
Parotid	Gynacomastia	KF ring
Testicular atrophy :	Other signs:	
Flapping tremor	PR: RR :	BP:

P/A :

Distension	Dilated veins	Scar/ Sinus
Ascites	Liver span	Spleen
Per rectal exam		
CVS	RS	CNS

Investigations :

Hb :	Tc :	Dc :
ESR :	Platelet count :	BT / CT
RBS :	Urea :	Creatinine :
P.smear :	Prothrombin time ;	INR
T.bil:	Direct :	Indirect :
SGOT :	SGPT :	SAP :
T.Protein :	Albumin :	Globulin
A/G :		
HbsAg :	Anti Hcv :	S.Ceruloplasmin :

ANA : Anti Sm Ab : AMA :

Anti LKM Ab : 24 hour Urine Copper :

Ascitic fluid :

T.Protein : Albumin : Cell count :

Cytology : SAAG ratio :

Ultrasound color doppler :

Liver size : Texure/ Nodule :

Spleen size : Collaterals :

OGD :

Esophageal varices :

Grade : No of Columns : Length :

Red Signs : Gastric Varices : PHG :

PHD :

Liver biopsy :

EVL :

Child pugh score :

Colonoscopy:

Erythema : colitis like : vascular lesions :

Rectal varix : hemorrhoids : colonic varix :

Others :

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