# A STUDY ON NATURAL HISTORY OF VARICEAL BLEED IN AN ERA OF SCLEROTHERAPY

Dissertation submitted to

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**D.M. BRANCH – IV MEDICAL GASTROENTEROLOGY**

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**CHENNAI – TAMILNADU**

# CERTIFICATE

This is to certify that the dissertation titled **"NATURAL HISTORY OF VARICEAL BLEED IN AN ERA OF SCLEROTHERAPY"** is the bonafide original work done by **S. JOYE VARGHESE** in partial fulfillment of the requirements for DM Branch – IV (Medical Gastroenterology) Examination of the Tamilnadu DR. M.G.R Medical University to be held in August 2007 under our supervision and guidance.


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# DECLARATION

I, **Dr. S. Joye Varghese,** solemnly declare that dissertation titled, **"Natural History of Variceal Bleed in an era of Sclerotherapy"** is the bonafide work done by me at Govt. Stanley Medical College and Hospital during the period January 2005 to June 2006 under the expert guidance and supervision of **Prof. V. Jayanthi MD, DM, Head of the Department,** Department of Medical Gastroenterology.

The dissertation is submitted to the **Tamil Nadu Dr. MGR Medical University** towards partial fulfillment of requirement for the award of **DM Degree (Branch IV) in Medical Gastroenterology.**

Place : Chennai

Date : 10.05.2007 **Dr. S. Joye Varghese**

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# CONTENTS

## INTRODUCTION

Portal hypertension manifesting as gastrointestinal bleed is common in 30% of cirrhotic patients, with a one year mortality of 50% after the initial bleed.[1-6] The greatest risk is during the first 48 to 72 hours and more than 50% of all early rebleed episodes occur within the first 10 days after cessation of active hemorrhage.[7-9]

While most of the reports on the variceal bleed pattern are from the West, little information is available from the Southern states of the Indian subcontinent. A preliminary observation from our center in 2003 had shown a low rebleed rate after the index bleed.[10] This study had a drawback of inclusion of bleeders who were already on treatment and there was probably a bias towards a low rebleed rate.

The present study was undertaken to prospectively assess the variceal bleed pattern and its attendant complications amongst cirrhotics with portal hypertension. Ethics committee of Institution approved the undertaking of the study.

## AIMS AND OBJECTIVES

1. To determine variceal pattern amongst south Indian patients with cirrhosis liver
2. To study the prevalence of recurrent bleed
3. To study the risk factors that predicts an index bleed and subsequent bleed.

# REVIEW OF LITERATURE

## Anatomic features portal venous system:

The portal venous system, formed by the confluence of the superior mesenteric vein and the splenic vein which drains the stomach, the large and small intestine, the pancreas, and the spleen. An important feature of this system is that a number of its tributaries also communicate with the systemic circulation. These include the intrinsic and extrinsic veins of the gastroesophageal junction; hemorrhoidal veins of the anal canal; paraumbilical veins and the recanalized falciform ligament; the splenic venous bed and the left renal vein; and the retroperitoneum.

In portal hypertension, these venous collaterals dilate and allow portal venous blood to return to the systemic circulation. Clinically, the most significant collaterals are the intrinsic veins of the gastroesophageal junction, which are located close to the mucosal surface. They are the collaterals most likely to bleed when dilated because of increased blood flow.

The veins of the gastroesophageal junction are classified as intrinsic, extrinsic, and venae comitantes. The intrinsic veins form a subepithelial and submucosal plexus starting at the gastric cardia (upper stomach) and running the length of the esophagus. In healthy persons, these veins drain into the extrinsic plexus through perforating veins 2 to 3 cm above the gastroesophageal junction. Flow through the

perforating veins is unidirectional toward the extrinsic plexus and systemic circulation. When portal hypertension develops, however, the valves of the perforating veins become incompetent and allow reversal of flow from the extrinsic to the intrinsic system.

Varices of the gastroesophageal junction usually are classified by location as esophageal or gastric. Esophageal varices consist of three or four large trunks that are further characterized by size. This classification is important because the larger the varix, the more likely it is to bleed. Gastric varices, on the other hand, are by convention classified only by location. Most likely to bleed are the isolated variceal clusters of the fundus, which often are caused by splenic vein thrombosis or spontaneous splenorenal collaterals.

## Pathophysiology of portal hypertension:

Portal pressure can be measured only angiographically and is expressed in terms of hepatic venous pressure gradient (HVPG). HVPG is the difference between the wedged hepatic venous pressure and the free hepatic venous pressure. The former is a reflection of sinusoidal pressure, and the latter is a correction for the effects of intra-abdominal pressure (eg, tense ascites). Portal pressure is directly related to

portal venous inflow and the degree of outflow resistance; it can be expressed in terms of Ohm's law as follows:

Portal pressure = portal venous inflow x outflow resistance

The initiating event in the development of portal hypertension is increased resistance to portal outflow. Some causes and sites of the increased resistance are listed below.

- Prehepatic
    - Splenic vein thrombosis
    - Portal vein thrombosis
    - Extrinsic compression of the portal vein
- Intrahepatic
    - Congenital hepatic fibrosis
    - Hepatic peliosis
    - Idiopathic portal hypertension
    - Sclerosing cholangitis

- Tuberculosis
- Schistosomiasis
- Primary biliary cirrhosis
- Alcoholic cirrhosis
- Hepatitis B virus–related and hepatitis C virus–related cirrhosis
- Wilson disease
- Hemachromatosis
- Alpha-1 antitrypsin deficiency
- Chronic active hepatitis
- Fulminant hepatitis

- Posthepatic
  - Budd-Chiari syndrome
  - Thrombosis of the inferior vena cava
  - Constrictive pericarditis
  - Venoocclusive disease of the liver

In cirrhosis, portal hypertension is aggravated by the increase in the portal venous inflow due to splanchnic vasodilation. When portal pressures rise, blood flow is diverted to venous collaterals that dilate to form varices. The likelihood that any one varix will rupture and bleed depends on its wall tension, which can be determined by the application of Poiseuille's and Laplace's laws. In practice, this means that a large, long varix with a high flow rate and a thin wall is most likely to rupture and bleed. Because it is not feasible to shorten a varix or increase its wall thickness, therapies for portal hypertension aim to decrease variceal flow. This decrease is achieved by reducing either portal venous inflow (eg, by splanchnic vasoconstriction) or resistance to portal outflow (eg, by creation of a shunt).

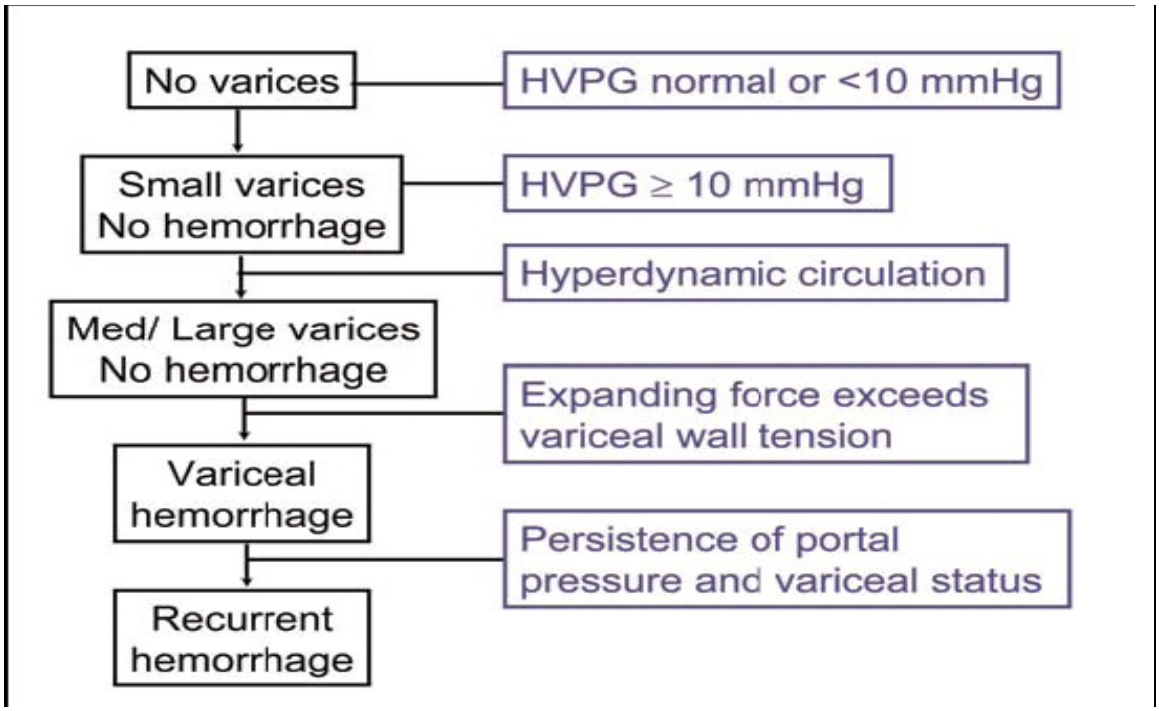
**Natural history of varices:**

The natural history of varices in cirrhotic patients with portal hypertension evolves from a patient without varices to the patient that develops varices to the patient that develops variceal hemorrhage. Varices and variceal hemorrhage are a direct consequence of portal hypertension. Gastroesophageal varices are present in approximately 50% of cirrhotic patients when endoscopy is performed at the time of the diagnosis of cirrhosis. Their presence correlates with the severity of liver disease; while only 40% of Child A patients has varices, they are present in 85% of Child C patients. (11) Patients with varices almost invariably have a portal

pressure (as determined by the hepatic venous pressure gradient [HVPG] of at least 12 mm Hg, while normal HVPG is 3–5 mm Hg. (4, 12) Initially varices are small, but they enlarge with increasing blood flow. When a varix enlarges and the tension in its wall exceeds the expanding force, rupture occurs, leading to the most deadly complication of cirrhosis, variceal hemorrhage. This complication has a high risk of recurrence. In patients without them, varices develop at a rate of 8% per year. (13,14) and factors associated with this progression are the presence of decompensated cirrhosis (Child B/C), alcoholic etiology, and presence of red wale marks at the time of baseline endoscopy.(13) Variceal hemorrhage occurs at a rate of 5%–15% per year and the most important predictor of hemorrhage is the size of varices, with the highest risk of first hemorrhage (15% per year) occurring in patients with large varices. Other predictors of hemorrhage are decompensated cirrhosis (Child B/C) and the presence of red wale marks on endoscopy. (15) Although bleeding from esophageal varices ceases spontaneously in up to 40% of patients, the mortality of an episode of variceal hemorrhage is of at least 20% at 6 weeks, and it occurs mostly in patients with severe liver disease and in those with early re-bleeding. Late rebleeding occurs in approximately 60% of untreated patients within 1–2 years of the index hemorrhage. (4,16)

Portal pressure directly can only be measured by invasive methods. The most commonly used technique involves the catheterization of the hepatic vein via a transfemural or a transjugular route. By subtracting the free hepatic vein pressure

from the wedged hepatic venous pressure, the hepatic vein pressure gradient (HVPG) can be calculated, which is an indirect but precise estimate of portal pressure. The normal upper limit of the HVPG is 5 mmHg. (12,13) Values above this limit denote portal hypertension.




Clinically significant portal hypertension (CSPH) indicates the pressure level at which a patient is at high risk of developing complications and therefore should receive prophylactic treatment. Varices do not occur and do not bleed if the HVPG is below a threshold value of 10-12 mmHg. As a consequence, the following definition of CSPH has been given at a recent international consensus workshop (20). “CSPH is defined by an increase in HVPG to a threshold above approximately 10 mmHg. The presence of varices, variceal hemorrhage, and/or ascites is indicative of the presence of CSPH”. Thus, the policy of identifying and monitoring patients with portal hypertension should be primarily targeted on patients with CSPH.

**Screening for esophageal varices:**

Effective prophylactic treatments to prevent variceal bleeding exist for patients with esophageal varices. (4) There are no reliable methods of predicting which cirrhotic patients will have esophageal varices without endoscopy.(17) An American Association for the Study of Liver Diseases guideline suggests that patients with Child's stage A liver cirrhosis and signs of portal hypertension, specifically a platelet count of less than 140,000/mm , and/or enlarged portal vein diameter of greater that 13 mm or those classified as Child's B or C at diagnosis should have screening endoscopy.(18) Patients with cholestatic disease may have portal hypertension with relatively preserved liver function and platelet counts. A retrospective study of 235 patients concluded that patients with either primary biliary cirrhosis or primary sclerosing cholangitis who have a platelet count 200/mm(4) , an albumin level 40 gm/L, and a bilirubin level 20 mmol/L should be screened for esophageal varices. (19) Other groups recommend screening for all patients diagnosed with cirrhosis.(20) The optimal surveillance intervals for esophageal varices have not been determined. For patients found to have no varices on ini-tial screening endoscopy, repeat endoscopy at 3-year intervals has been suggested, whereas patients with small varices should undergo endoscopy in 1 to 2 years. (20) Esopha- geal varices may grow faster in patients with cirrhosis secondary to alcohol abuse or severe liver impairment and in those with endoscopic stigmata of high risk (''red wale markings''); this subgroup of patients

should undergo yearly upper endoscopy.

Concerning abdominal ultrasound and Doppler studies, inter-observer and inter-equipment variability limit their applicability in clinical practice. Thus, the current recommendation (20) is that the accuracy of non-invasive tests (such as Doppler ultrasound) for the diagnosis of clinically significant portal hypertension should be further assessed before their use can be recommended in clinical practice. As a consequence, upper GI endoscopy is the main tool used for screening and monitoring patients.

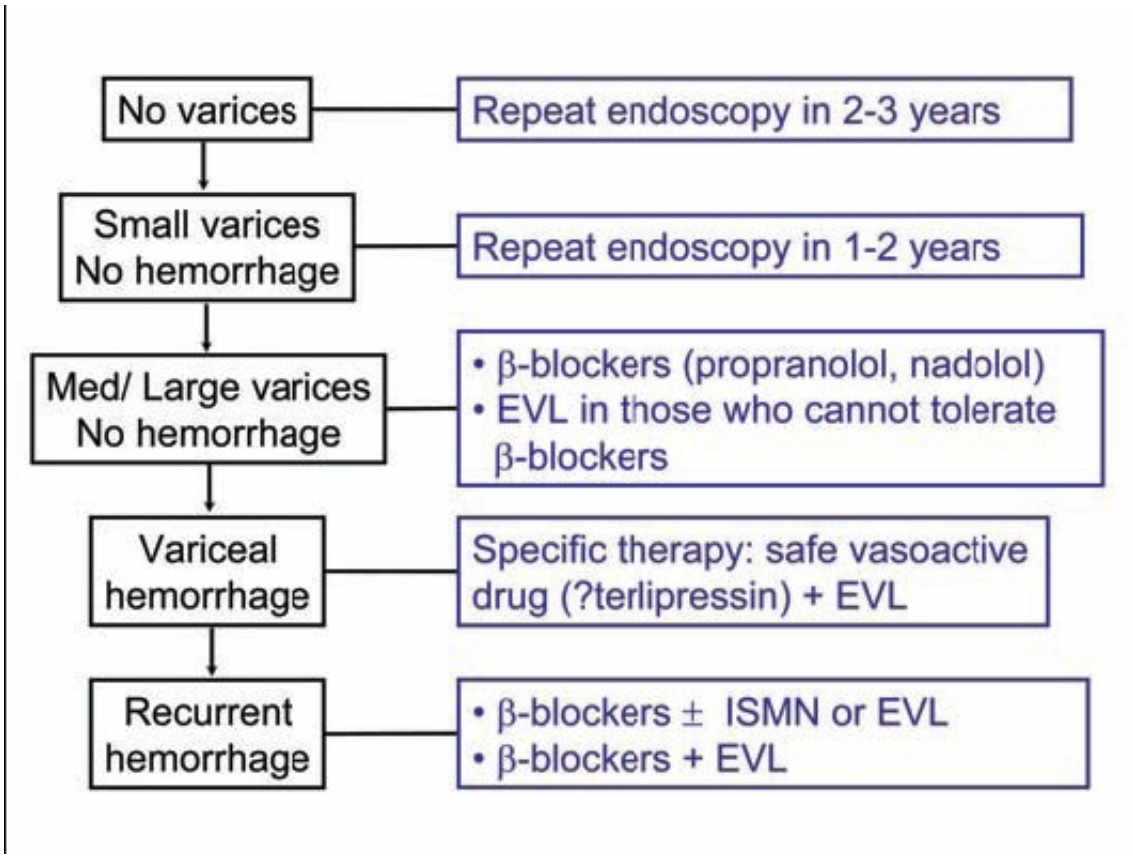
**Preventing the development of varices:**

The reduction in portal pressure induced by b-adrenergic blockers has been shown experimentally to prevent the development of portosystemic collaterals. (22) Endoscopic screening for varices should be performed in all patients with cirrhosis and, in those patients without varices, b-blockers are not recommended. (21) In these patients, endoscopy should be repeated in 2–3 years, sooner if there is evidence of hepatic decompensation.

**Preventing first variceal hemorrhage in patents with varices:**

Current guidelines recommend prophylactic therapy with nonselective b-blockers (propranolol, nadolol) to prevent first variceal hemorrhage in cirrhotic patients with medium- to large-sized esophageal varices on screening endoscopy. Although the risk of first hemorrhage with b-blocker therapy is significantly decreased, it is not eliminated. Furthermore, b-blockers cause side effects in ~20% of cases, leading to discontinuation of treatment in ~12% of patients. (23)

EVL is slightly better than b-blockers for prevention of a first variceal bleed. However, given controversial results from incomplete trials, the recommendations of the Baveno conference still stand, that is, that nonselective b-blockers are first line therapy in the prevention of first variceal hemorrhage and EVL should be offered to patients with large varices who are not candidates for long-term b-blocker therapy. (21) An additional recommendation should be to initiate EVL before or promptly after discontinuation of b-blockers in those who cannot tolerate these drugs. Early beta-blocker therapy may slow the rate of growth of small esophageal varices. (24) Endoscopic sclerotherapy (EST) is not recommended for primary prophylaxis. (25,26) While several studies have shown benefit, a well-done US study showed an increased mortality rate in the treated group.




**Lab Studies:**

- Complete blood count: Results may show anemia, leucopenia, and thrombocytopenia in patients with cirrhosis. Anemia may be secondary to bleeding, nutritional deficiencies, or bone marrow suppression secondary to alcoholism. Many patients with portal hypertension have some degree of hypersplenism. The hematocrit value may be low in patients with upper abdominal bleeding.

- Type and crossmatch blood and reserve 6 units of packed red blood cells.
- Prothrombin time: Because the coagulation factors involved in this test are synthesized by the liver, impairment of the liver function may result in a prolonged prothrombin time.
- Liver function tests: A mild elevation of the plasma activity of aspartate aminotransferase (AST) and alanine aminotransferase (ALT) may occur in cirrhosis, although activity may be normal.
- Blood urea, creatinine, and electrolytes: Blood urea and creatinine levels may be elevated in patients with esophageal bleeding. Drug treatment, cirrhosis, ascites, and blood loss may contribute to changes in the serum electrolytes of these patients.
- Arterial blood gas and pH measurements
- Hepatic serology helps in the assessment of the cause of cirrhosis.

**Imaging Studies:**

- Ultrasound of the upper abdomen may be indicated, especially if biliary obstruction or liver cancer is suspected.

**Other Tests:**

- Rectal examination: Obtain a stool sample for visual inspection. A black, soft, tarry stool on the gloved examining finger suggests upper GI bleeding

**Treating acute variceal hemorrhage:**

Regarding non-specific management, current guidelines recommend prophylactic antibiotic therapy for cirrhotic patients admitted with acute variceal hemorrhage and should be instituted from admission. (21) The recommended specific management consists of the combination of endoscopic therapy plus a safe vasoactive drug (terlipressin or analogues, somatostatin or analogues (21). The advantage of these drugs is that they can be started at admission and before diagnostic/ therapeutic endoscopy and continued for 2–5 days to prevent early variceal re-bleeding. Baik et al. (28) suggested that 2 mg IV terlipressin may be of greater benefit than somatostatin and its analogues. Although both drugs decreased HVPG significantly, the effect of terlipressin was sustained over the 25-minute duration of the study while the effect of octreotide was transient having shown a maximal effect at the first minute (decrease of 45% from baseline); however, the HVPG had returned to baseline as of the 5-minute time point.

Regarding the best endoscopic therapy for the control of acute variceal hemorrhage, a meta-analysis of 10 randomized controlled trials shows an almost significant benefit of EVL in the initial control of bleeding compared to sclerotherapy. (27) and also sclerotherapy is associated with an increase in HVPG

that was maintained throughout the 5-day period of the study, while EVL was associated with only a transient increase in HVPG that returned to pretreatment values within 48 hours. (29) Therefore, in the Baveno consensus report, EVL is the recommended form of endoscopic therapy for acute esophageal variceal bleeding although sclerotherapy is recommended if EVL is technically difficult. (21) Failures of initial therapy with combined pharmacological and endoscopic therapy are best managed by a second attempt at endoscopic therapy or, in the case of fundal gastric varices, by the transjugular intrahepatic portosystemic shunt (TIPS). (21)

**Preventing recurrent variceal hemorrhage:**

Either combination pharmacological therapy (nonselective b-blockers plus nitrates) or EVL are considered the therapy of choice in the prevention of variceal re-bleeding. The choice depends on tolerance and local expertise. However, with either of these therapies, re-bleeding rates are still quite high (30%–42% in studies of b-blockers plus nitrates; 20%–43% with EVL). (16) The lowest re-bleeding rates of 7%–13% have been described in studies on pharmacological therapy in which HVPG decreases by >20% from baseline or to levels below 12 mm Hg (16) Randomized controlled trials show combining EVL and b-blockers significantly reduces re-bleeding rates than EVL alone. (30,31) Additionally, 1-year variceal recurrence was lower in the EVL + nadolol group (54%) than in the EVL group

(77%). Therefore the current recommendation is still to use EVL or b-blocker + nitrates as first line therapy, recognizing that combination EVL+ b-blocker may be a more effective therapy. (21)

Side effects of EVL include hemorrhage from ulcers, chest pain, dysphagia, and odynophagia. Because gastric acid may exacerbate post-EVL ulcers, acid suppressors may reduce EVLrelated side effects. (32)

In patients who fail combined endoscopic and pharmacological treatment for prevention of re-bleeding, TIPS or surgical shunts should be considered, depending on local availability and the surgical candidacy of the patient. Patients with decompensated cirrhosis are not candidates for shunt therapy and should be evaluated for liver transplantation.

**Endoscopic Sclerotherapy:**

Endoscopic sclerotherapy for variceal bleeding, although described in 1939 (33), was "rediscovered" in the late 1970s. Soon it became evident that ongoing hemorrhage from a varix could be stopped by the injection of various chemical agents, that this form of intervention decreased the volume of blood transfused, and that additional injection sessions decreased the number of episodes of recurrent bleeding. Sclerotherapy may sometimes be equal or perhaps even superior to portacaval or selective splenorenal shunt surgery in terms of survival and the preservation of hepatic function (34-36). The results of one trial (37) indicate that endoscopic sclerotherapy decreases the mortality for patients with cirrhosis and

variceal bleeding; however, another trial (38) did not find a decrease in mortality. A meta-analysis of seven trials revealed that overall survival for patients with variceal bleeding was improved by sclerotherapy (39). Thus, it appeared that a definitive treatment for this major complication of portal hypertension had been found. This is not entirely true, but sclerotherapy has become a major technique used in the management of variceal hemorrhage, and it has benefited patients greatly.

However, endoscopic sclerotherapy has limitations. The injection of a noxious agent into any segment of the human vascular system raises the possibility of untoward effects in organs at a distance from the primary site of injection. The potential risk for such complications would depend to an extent on variceal anatomy. Unfortunately, only a few studies (40-42) exist of normal esophageal venous and variceal anatomy and of the nature of blood flow in these structures. Those studies that are available suggest that an injected sclerosing agent may reach virtually any organ. This has been substantiated by many reports of untoward events after sclerotherapy, some with serious consequences, in organ systems other than the esophagus. In particular, an appreciable risk exists for sepsis after sclerotherapy. Although these "systemic" complications are relatively rare, they represent an important shortcoming for endoscopic sclerotherapy.

Endoscopic sclerotherapy is less than ideal as a therapeutic measure because tissue

injury is fundamental to its mechanisms of action. Once injected, the action of the chemical agent is, to a certain extent, uncontrollable and unpredictable. This accounts for various local complications, including perforation, stricture formation, and ulceration. The destructive basis of sclerotherapy is emphasized by the fact that ulcers at injection sites are expected to occur in all patients. The difference between an ulcer as a desirable consequence of therapy and one that represents a true complication is merely a matter of degree and the clinical behavior of the lesion. Unfortunately, tissue damage probably also occurs with variceal ligation, although to a lesser degree than with sclerotherapy

**Endoscopic Variceal Ligation:**

Endoscopic variceal ligation of esophageal varices is based on a technique developed in the 1950s for band ligation of hemorrhoids. As originally described by Stiegmann and colleagues (43), use of this technique for esophageal varices involves the mechanical ligation and strangulation of variceal channels by application of small, elastic "O" rings. Several rings must be applied at various sites; because each ring must be loaded individually on the end of the endoscope, an overtube is used to allow rapid and repeated passage of the endoscope. Actual application of the ring to a varix is by means of an ingenious device attached to the distal end of a standard endoscope. Although a sequence of steps is required, most endoscopists find the technique for band ligation to be less demanding than that for sclerotherapy.

**Sclerotherapy Compared with Ligation:**

The work of Stiegmann and colleagues (44-48) on endoscopic variceal ligation may serve as a model for the development of new technology. Single-arm trials by this group have shown that variceal ligation is comparable to endoscopic sclerotherapy in terms of control of variceal hemorrhage and the prevention of recurrent bleeding, but that variceal ligation has substantially less morbidity.

Although of good quality and credible, this work must be corroborated by other investigators. In the randomized, controlled trial reported by Laine and colleagues (49), there was no difference between variceal ligation and sclerotherapy with respect to recurrent variceal bleeding, volume of blood transfused, length of hospitalization, and survival. Compared with patients who had sclerotherapy, however, those treated with ligation had higher Child-Pugh scores as well as varices of a more advanced endoscopic grade. In the only other randomized, controlled trial of ligation compared with sclerotherapy, Stiegmann and coworkers (50) showed a survival advantage for variceal ligation. In this study, patients were evenly matched for Child-Pugh score and variceal grade at endoscopy.

In the study of Laine and colleagues (49), variceal ligation was superior to sclerotherapy with respect to local esophageal complications, especially stricture formation. However, the percentage of patients (33%) who developed an esophageal stricture as a result of sclerotherapy is remarkably high in this study. This is difficult to explain but may be due to the use of a relatively high concentration of the sclerosing agent. It is probable that the use of a less potent solution would have resulted in fewer strictures, although this might not have prevented recurrent bleeding and might not have decreased the number of treatment sessions required for variceal eradication. The technique of variceal ligation would seem to be inherently safe, but Laine and colleagues did encounter one patient who had an esophageal injury that appeared to be due to placement of the overtube. Although the risk for a "systemic" complication after variceal ligation should be negligible, bacteremia has been reported (51). Variceal ligation also required statistically fewer treatment sessions for eradication of varices.

**Balloon tamponade:**

Balloon tamponade achieves control of variceal bleeding by direct pressure on the varices and can be life saving in the patient who presents with massive haemorrhage. In experienced hands it is highly effective, with control of bleeding

in 90% of cases. (52) However, up to 50% of patients rebleed when the tube is deflated, and there is an associated complication rate of 25-30% (53) Serious complications such as oesophageal perforation or ulceration and aspiration pneumonia may occur in up to 15% of patients.

The gastric balloon is the most important factor for controlling bleeding. The balloon is inflated with 120-200 ml water (containing a small amount of radiographic contrast to enable it to be seen more easily on radiographs) and needs to be placed close to the oesophagogastric junction to arrest cephalad blood flow. We use a tube with both gastric and oesophageal balloons (Sengstaken-Blakemore) but inflate the oesophageal balloons only if bleeding is not controlled. If gastric varices are the source of haemorrhage a tube with a single large (600 ml) gastric balloon (Linton- Nachlas) is more effective in stopping haemorrhage.(54) The balloon should not be inflated for more than 18 hours. Alternative, definitive treatment must be planned for when the balloon is deflated

**Transjugular intrahepatic portosystemic shunt:**

TIPS is an angiographically created shunt between hepatic and portal veins that is kept open by placement of a fenestrated metal stent. It effectively decompresses the portal system, controlling active variceal bleeding over 90% of the time and

achieving a mortality rate of less than 10%, even in critically ill patients (55) Immediate complications include secondary bleeding and, in 20% of cases, worsening encephalopathy. The most common long-term complications are stent stenosis or occlusion that requires balloon angioplasty. Causes of bleeding and recurrent portal hypertension after TIPS are summarized below.

**Causes of bleeding and recurrent portal hypertension after TIPS:**

Stent dysfunction

- Thrombosis
- Retraction
- Displacement
- Stenosis

Severe right-sided heart failure

Hemobilia

Persistent gastric varices

- Associated with spontaneous splenorenal collaterals
- Associated with massive splenomegaly

As a consequence, TIPS is primarily used as rescue therapy when pharmacologic and endoscopic treatment of acute bleeding is unsuccessful. (56)

**Prevention of complications and deterioration in liver function:**

*Infection Control and Treatment:*

Bacterial infections have been documented into 35-66% of patients with cirrhosis who have variceal bleeding, with an incidence of SBP ranging from 7-15%. However if only patients with ascites and gastrointestinal bleeding are considered, the incidence of SBP is very high. A recent meta-analysis has demonstrated that antibiotic prophylaxis significantly increased the mean survival rate (9.1% mean improvement rate, 95% CI: 2.9-15.3,p=. 004) and also increased the mean percentage of patients free of infection (32% mean improvement rate, 95% confidence interval: 22-42, p<. 001) (57). Finally our group has recently shown that bacterial infection, diagnosed on admission, is an independent prognostic

factor of failure to control bleeding or early rebleeding (58). These data may support a role of bacterial infection in the initiation of variceal bleeding (59). All cirrhotics with upper gastrointestinal bleeding should receive prophylactic antibiotics whether sepsis is suspected or not. The optimal regimen is yet to be decided but oral or intravenous quinolones have been used.

*Ascites and renal function:*

Renal failure may be precipitated by a variceal bleed, usually due to a combination of acute tubular necrosis, and hepatorenal syndrome (HRS) associated with deterioration in liver function and sepsis. HRS is associated with an over 95% mortality. Thus any iatrogenic precipitants must be avoided.

The intravascular volume should be maintained preferably with Human Albumin Solution or blood initially. Normal saline should be avoided as it may cause further ascites formation. Catheterisation of the bladder and hourly urine output measurement is mandatory and nephrotoxic drugs should be avoided, especially aminoglycosides and non-steroidal drugs.

Dopamine was the first drug used due its vasodilator effect when given in subpressor doses. Dopamine is frequently prescribed to patients with renal impairment, and yet no studies have ever shown any convincing benefit (60,61) It

is our impression that occasionally a patient responds with an increase in urine output. It is therefore our practice to give a 12-hour trial of dopamine, and stop treatment if there has been no improvement of urine output.

Increasing ascites may occur shortly after bleeding, but should not be the main focus of fluid and electrolyte management until bleeding has stopped and the intravascular volume is stable. If there is a rising urea and creatinine, all diuretics should be stopped, and paracentesis performed if the abdomen becomes uncomfortable, re-infusing 8 gr. of albumin for every litre removed.

When the patient has stopped bleeding for 24 hours, nasogastric feeding can be commenced with low sodium feed. This avoids the need for maintenance fluid, and removes the risk of line sepsis.

An unexplained rise in creatinine and urea may indicate sepsis. Evidence of sepsis should be sought by blood, ascitic, cannulae, and urine culture, and non-nephrotoxic broad-spectrum antibiotics commenced, regardless of evidence of sepsis. An undiagnosed delay in effective treatment of infection may increase mortality. In advanced cirrhosis, endotoxins and cytokines play an increasingly important role in advancing the hyperdynamic circulation and worsening renal function (62)

There is now increasing evidence for the use of vasopressin analogues in this condition, and the beneficial effect of terlipressin with respect to bleeding and survival in trials to date may be through the prevention of this catastrophic complication (63-65)

*Porto-systemic Encephalopathy:*

The precipitant factors include: haemorrhage, sepsis, sedative drugs, constipation, dehydration, and electrolyte imbalance. These should be evaluated and corrected. Hypokalaemia, hypomagnesaemia and hypoglycaemia which may precipitate encephalopathy and should be aggressively corrected (e.g. a patient with ascites and a serum potassium of 3.0mmol/L is likely to require in excess of 100 mmol over 24 hours). As soon as the patient is taking oral fluid, lactulose 5-10mls QDS can be started. Phosphate enemas are also useful.

*Alcohol withdrawal:*

It is important to be alert to the possibility of withdrawal from the patient's history. Encephalopathy and withdrawal may co-exist, and careful use of benzodiazepines may be required. Benzodiazepines or oral clormethiazole can be used.

*Nutrition:*

Only a few cirrhotics are not malnourished (66), particularly with severe liver disease. Often they do not want to eat, are “nil by mouth” because of investigations, and the food itself maybe "unappealing". Thus exacerbation of malnutrition is common.

A fine bore nasogastric tube should be passed 24 hours after cessation of bleeding to commence feeding commenced. There is no evidence that this may precipitate a variceal and it allows treatment of encephalopathy in comatose patients and makes fluid management easier. It is extremely rare that parental nutrition is required.

Vitamin replacement: All patients with a significant alcoholic history should be assumed to be folate and thiamine deficient, and be given at least three doses of the latter intravenously. It is easier and more practical to assume all such patients are vitamin deficient rather than delay treatment whilst awaiting red cell transketolase activity levels.

*Transfer of the Patient with Bleeding Varices and Use of Balloon Tamponade:*

Inter-hospital transfer should not be attempted unless the bleeding has been controlled, either with vasopressor agents/endoscopic therapy or tamponade. If there is any suggestion of continued blood loss, and the source is known to be variceal, then a modified Sengstaken tube must be inserted prior to transfer. (i.e. with an oesophageal aspiration channel such as the Minnesota Tube)

**Duodenal varices:**

Duodenal varices occur in about 0.4% in all patients with portal hypertension and account for one third of bleeding episodes from ectopic varices. Early detection is important, as duodenal varices are a potential source of massive hemorrhage. At upper gastrointestinal endoscopy, an uninitiated observer may misinterpret bleeding from duodenal varices as that from duodenal ulcer. These should be considered in all patients with duodenal tumoral lesions and suspected portal hypertension. In this context, duodenal biopsy can be dangerous and should be avoided. A diminution in the volume of the duodenal varices with inspiratory movements may help in the differential diagnosis during endoscopy.

The duodenal bulb is the most common site of duodenal varices, the second portion of the duodenum appears to be the next most common site but duodenal varices in the other portions are rare. Hashizume et al. studied these varices

angiographically and histopathologically; and found that the duodenal varix consisted of a single vessel with afferent and efferent vessels, forming a portosystemic shunt in the retroperitoneum. The varix traversed the duodenum and was present in the submucosal layer of the posterior wall; while the afferent vessel was the superior or inferior pancreaticoduodenal vein originating in the portal vein trunk or superior mesenteric vein, and the efferent vein drained into the inferior vena cava. They have also been reported at the site of previous duodenal operations and the resultant adhesions and after endoscopic sclerotherapy. Duodenal varices are more common in patients having extrahepatic portal vein obstruction and in those with thrombosed portosystemic shunts.

Apart from endoscopy, hypotonic duodenography, ultrasonography, computed tomography, venous phase of superior mesenteric angiography, and percutaneous transhepatic portography have been used to diagnose duodenal varices.

Medical therapies, including vasopressin and octreotide may have limited success in controlling active duodenal variceal bleeding. Endoscopic sclerotherapy or endoscopic variceal ligations are the main treatment modalities. Embolization and transjugular intrahepatic portosystemic shunt are the therapeutic alternatives, if endoscopic sclerotherapy or variceal ligation fails to control the bleeding. When conservative measures cannot control the hemorrhage, emergency laparotomy may be indicated. Duodenal varix suture ligation or resection results in a high rate of

rebleeding. End-to-side portacaval shunt may be effective. An arteriovenous fistula requires resection of the paramural varix and surgical occlusion. In view of the difficulty during the duodenal mobilization and the precarious condition of patient, it is not surprising that the operative mortality is high.

**Jejunal and ileal varices:**

A triad of portal hypertension (generally due to liver cirrhosis), history of abdominal surgery, and hematochezia without hematemesis characterizes small intestinal varices. Bleeding from varices may present with vesical varices and gross hematuria if an intestinal segment is used for an augmentation cystoplasty. A history of abdominal surgery appears to predispose the development of ectopic varices (portosystemic communication) in adhesions. Possible physiological origins of this entity were studied in Edward's demonstration of network of fine communication between the parietal surface of the viscera and the posterior abdominal wall, arising in the embryo due to the juxtaposition of the developing systemic and visceral venous plexus. Formation of collaterals, de novo, is unlikely if the anatomy is undisturbed. In some cases no cause can be found. Histological examination demonstrates a massive varicose vein and several dilated veins in the submucosa. Although rare, bleeding from small bowel varices is associated with a high mortality as accurate preoperative diagnosis is often difficult. Detection of these varices has been a challenging task and several invasive diagnostic techniques such as enteroclysis, Tc-99m RBC studies, venous phase of mesenteric

arteriography, enteroscopy, color flow Doppler ultrasound and magnetic resonance angiography have been used for this purpose. Intraoperative Sonde enteroscopy is safe and effective, providing complete visualization of the small-bowel mucosa without enterotomy while avoiding the trauma that can be caused by push endoscopy. It is the diagnostic assessment of choice. Medical therapy, including vasopressin infusion via the superior mesenteric artery, is often useful in controlling acute variceal bleeding. Percutaneous transhepatic embolization and transjugular intrahepatic portosystemic shunt are the therapeutic alternatives. Surgical treatment consists of lysis of adhesions and bowel resection combined with portosystemic shunt, under the presumption that the portal pressure in these patients has been partially decompressed through these spontaneous shunts and may increase significantly after their surgical division. Patients with excellent hepatic reserve survive and have no further gastrointestinal bleeding.

**Colonic varices:**

Colonic variceal bleeding is a rarity and is most commonly due to portal hypertension, with local mesenteric vein obstruction constituting a rare cause. The true prevalence of colonic varices is not known, but Feldman et al. found an

incidence of 0.07% in autopsy material. Esophageal varices were present in approximately half of the group with colonic varices. Bleeding has been reported to occur in 2.5% of patients attending sclerotherapy sessions for esophageal varices. In patients with portal hypertension the coronary azygous system was the primary portosystemic channel in at least half of the cases, but in a quarter of cases it was the inferior mesenteric-internal iliac system. Possible etiologies of this condition may be esophageal transection and devascularization and extensive thrombosis of the portal vein resulting in obliteration of the coronary-azygous anastomotic system. In such a situation, other potential sites of porto-systemic anastomoses, such as that in the colon, may open, leading to development of colonic varices. Idiopathic/primary, familial, secondary to splenic vein thrombosis and adhesion-related colonic varices without portal hypertension have also been reported. Varices of the colon are usually segmental, involving predominantly (66%) the distribution of inferior mesenteric vein and less frequently in the distribution of superior mesenteric area, and never confined to transverse colon. Diffuse variceal involvement of the colon is uncommon and implies an unknown cause. In case of colonic varices the differential diagnosis should include portal hypertension with chronic liver disease, portal vein thrombosis, vascular anomalies or postoperative complications. If this entity is not considered, a rectal or colonic biopsy may lead to brisk and dangerous bleeding. Apparent similarity of radiological and endoscopic appearance of varices to polyps, misdiagnosis and inappropriate biopsy remain the potential pitfalls. Colonoscopist visualizes these

varices as serpiginious to nodular, often bluish submucous lesions. They are often missed on colonoscopy due to collapse of varices during periods of hypotension or because of increase in the intraluminal pressure due to air insufflation during the endoscopic examination. Sensitivity of colonoscopy is greatly reduced during periods of active bleeding and in the absence of good bowel preparation.

In cases where the cause of lower GI bleeding is not clear, even after colonoscopy; venous phase of mesenteric angiogram and scintigraphic studies may be useful. If doubt persists, intraoperative colonoscopy may be useful to pinpoint the problem. Conservative therapy consists of vasopressin and somatostatin analogue, which may be useful in the control of bleeding. Sclerotherapy using a colonoscope and transjugular intrahepatic portosystemic shunt are other therapeutic alternatives. The choice of surgical therapy in portal hypertension is portal decompression and not colonic resection; as colectomy is associated with significantly greater mortality due to risk of infection and considerable technical difficulty of this surgery in the presence of portal hypertension.

**Anorectal varices:**

Anorectal varices are a rare cause of rectal bleeding and are often erroneously diagnosed as bleeding hemorrhoids. Although rare, rectum is the most common site of lower gastrointestinal varices. Rectal varices occur due to high pressure in

the inferior mesenteric venous system in patients with portal hypertension. Bleeding from them is uncommon, and often mild and self-limiting, but rarely it can be fatal. It is equally important to be aware of the presence of rectal varices in case rectal biopsy is needed in patients with portal hypertension. The reported incidence of rectal varices ranges from 40 to 89.3%. No correlation has been found between the presence of anorectal varices and the Child's grade of cirrhosis, intrahepatic V/s extrahepatic causes of portal venous obstruction, the grade of esophageal varices, the presence of gastric varices, portal hypertensive gastropathy, or whether or not patients received sclerotherapy. Identifying the source of lower gastrointestinal hemorrhage in patients with chronic liver disease and portal hypertension can be challenging but the differential diagnosis between hemorrhoids and anorectal varices has been elucidated in many studies. It has also been documented that the prevalence of hemorrhoids is not increased in patients with portal hypertension and their presence is unrelated to the degree of portal hypertension. A careful examination is essential to prevent misdiagnosis and inappropriate and inadvertent treatment like surgical excision of varices in mistake for hemorrhoids, with disastrous results. Anorectoscopy is the initial investigation of choice. Rectal endoscopic ultrasonography, transvaginal sonography and magnetic resonance imaging are useful in detecting the presence and number of rectal varices. The principal emergency treatment is endoscopic sclerotherapy or endoscopic ligation, failing which surgical ligation should be performed. Before the advent of transjugular intrahepatic portosystemic shunt (current choice of

treatment), a portosystemic shunt, preferably between the inferior mesenteric vein and the vena cava or renal vein, was the treatment of choice. Transjugular embolization of the inferior mesenteric vein is an alternative to TIPS, where TIPS is not feasible.

**Stomal varices:**

Variceal bleeding from enterostomy is an unusual complication of portal hypertension and represents a cause of recurrent or intractable gastrointestinal bleeding. Presence of caput medusae/varices developing around a stoma may herald the presence of mild to moderate portal hypertension before other signs of hepatic decompensation are evident. Once variceal communications have been formed between the portal venous system of the gut and subcutaneous systemic circulation, heavy bleeding from dilated venous plexus may occur spontaneously or from microtrauma. In a review, the average interval found was 48 months for ileostomies, 38 months for ileal conduits and 23 months for patients with a colostomy. Proper diagnosis requires careful inspection of the muco-cutaneous region of the stoma for venous bleeding sites and endoscopy examination of the stoma to rule out the presence of recurrent bowel disease or other lesions like arteriovenous malformations, polyp or Crohn's disease. The emergent treatment of bleeding of the colostomy must combine several methods, quite often consecutively: local compression, ligation, and sclerotherapy. Palliative local measures, like suture ligature or sclerotherapy, however, remain the treatment of

choice in the high-risk, cirrhotic patient who is unlikely to survive a major operation and may increase the interval between bleeding episodes and decrease the severity of bleeding. The hemorrhage can be managed temporarily in most patients with local measures. Once bleeding is controlled, the treatment must be primarily medical (hygienic and dietary habits, b-adrenergic blocking agents), but complementary surgery is invariably necessary because of recurrence of bleeding. There is no consensus on which of the various surgical options is best, but by and large, the type of further surgical treatment is determined by the severity of the underlying liver disease and the patient's life expectancy. Mucocutaneous disconnection (MCD) is simple, quick, repeatable and associated with a lower morbidity and intraoperative blood loss than stomal relocation. In the select group of patients that cannot be managed conservatively, MCD is favored and relocation considered only if MCD is technically impossible i.e. improperly placed stoma, symptomatic peristomal hernias and those with poor appliance fit. It should be kept in mind that repeated use of local operative procedures leads to the formation of scar tissue and causes problems in the care of the stoma. Although stomal manipulation is the most commonly performed procedure, portosystemic shunting has the lowest incidence of both rebleeding and need for additional procedures and provides the longest mean postoperative survival and is the choice in patients who are good surgical candidates. In particular, the absence of postoperative encephalopathy in the ileostomy group may be attributed to the absence of colon, the major source of bacteria generated nitrogenous products. Transjugular

intrahepatic portosystemic shunt and stomal varices embolization are effective alternatives in case of recurrent bleeding of stomal varices. The overall prognosis mainly depends on the function of the liver, the deterioration of which is accelerated by the successive hemorrhagic accidents. Particular attention should be paid to stoma care and the prevention of trauma from appliances.

**Biliary varices**

Gallbladder varices are often seen in portal hypertension, more often in extra hepatic portal vein obstruction patients. Gallbladder varices do not correlate with size of esophageal varices, number of sessions of sclerotherapy, presence or absence of gastric varices, portal gastropathy, Child Pugh grade or splenorenal shunt placement. These collaterals cause some gallbladder stasis but do not impede gallbladder function and hence seem unlikely to contribute to gallstone formation. Their clinical significance is their propensity to bleed during biliary surgery; thus, the operating surgeon should be aware of them. The color flow Doppler is the gold standard procedure for the diagnosis, although angiography, computerized tomography and magnetic resonance have also been reported. Bile duct varices are seen more frequently in left hepatic duct, possibly due to the joining of umbilical vein to the left branch of portal vein adjacent to the left hepatic vein. The resultant filling defect in the ERCP has to be differentiated from sclerosing cholangitis and malignancy. Due to their propensity to bleed, balloon dilatation is probably best avoided in these patients and placement of pigtail

biliary endoprostheses is preferred over straight stents with side flaps. Usually biliary varices are found incidentally during imaging, but their presence calls for a search for portal vein thrombosis. Rarely they can give rise to obstructive jaundice or haemobilia.

**Intraperitoneal hemorrhage from ectopic varices:**

Intraperitoneal hemorrhage from ectopic varices is a rare occurrence. In cirrhotic patients, sudden onset of abdominal pain in combination with hypotension and falling hematocrit in the absence of external blood loss should result in ultrasonography of the abdomen. The main differential diagnosis is acute pancreatitis. Any free fluid present should be aspirated and when blood is encountered the patient must be operated upon immediately. Spontaneous hemorrhage from anterior abdominal wall varices has also been documented into the rectus abdominus muscle and peritoneal cavity. Exploratory laparotomy and suture ligation of the bleeding varix seems to give the greatest likelihood of survival. Angiography with special attention to the venous phase may demonstrate the varices, in addition, vasopressin infusion in the superior mesenteric artery can be tried, which may permit stabilizing the patient before surgery. Patient's remaining liver function and the ability to withstand surgery determine the ultimate prognosis.

**Cutaneous variceal bleeding:**

In portal hypertension, three types of cutaneous portosystemic collaterals may develop the 'classical' Caput Medusae, enterostomal varices and scar or adhesion-related abdominal collaterals. Very few cases have been documented of a varicose umbilical vein with external hemorrhage significant enough to cause hemodynamic instability. Coagulopathy and hemorrhagic shock, ending in a fatality may complicate the clinical course. Local measures (direct pressure, suture ligation and sclerotherapy) and medical therapy should be applied early in the resuscitation of the patient. Once stable, definitive treatment has to be instituted otherwise rebleeding is a certainty. Transjugular intrahepatic portosystemic shunt, umbilical vein embolization and mesocaval shunt surgery have all shown good results, with stoppage of bleeding and disappearance of cutaneous varices.

**Miscellaneous:**

Upper esophageal varices occur infrequently and may rarely cause massive upper gastrointestinal hemorrhage. This case serves to stress the importance of a through examination of the cervical portion of the esophagus during routine endoscopy. Varices of the gastric antrum are seen in a small proportion of patients and are distributed equally amongst the etiologies of portal hypertension. They rarely bleed and may be ignored during sclerotherapy of esophageal varices, however, if required, sclerotherapy is the treatment of choice. Rarely, idiopathic varices have been reported throughout the gastrointestinal tract. Significant varices can occur

outside the gastrointestinal tract and have been described in kidney, lungs, tracheobronchial tree, mediastinum and vagina; giving rise to unusual hemorrhage as well as diagnostic difficulties on imaging.

## MATERIALS AND METHODS

The study group consisted of cirrhotic patients with portal hypertension (confirmed by ultra sound and Doppler study) registered and followed up at the liver clinic between January and June 2005. Patients who were on follow up for a minimum of one year until June 2006 were considered for analysis.

The following data were obtained at entry of the study:

**Age of the patient:**

**Gender of the patient:**

**Duration of illness:** i.e. duration in months up to the time of registration

**Details of treatment prior to registration** (as a clue to duration of illness). In asymptomatic individuals, the date of confirmed diagnosis on ultrasound was considered as the date of first presentation.

**Etiology of cirrhosis** was arrived based on history of alcohol intake including quantity & total duration of consumption; blood for viral serology (HBsAg & HBV DNA assay for hepatitis B and HCV RNA & Anti-HCV for hepatitis C); serum caeruloplasmin (< 20mg%), presence of Kayser Fleischer ring and 24 hours urine copper estimation (>100mg%) for Wilson's disease; and antinuclear antibody, hyper gammaglobulinemia (>3.5gm%) for autoimmune related cirrhosis.

Apart from details of past blood transfusion, surgery, family members with liver disease, details of **associated co-morbid illness** were also recorded. Diabetes mellitus was diagnosed when the fasting blood sugar was greater than 120 mg% or a postprandial value exceeded 200mg%; essential hypertension when blood pressure was more than 130/85 mm of Hg; hypothyroid state when T3 & T4 levels were low and with an elevated TSH. Renal disease was considered when the

blood urea and serum creatinine values were greater than 40mg/dL and 0.9 mg/dL respectively.

**Child Turcot Pugh (CTP) score** was applied to grade the severity of cirrhosis. CTP score is based on serum bilirubin, serum protein, ascites, prothrombin time and hepatic encephalopathy.

| | Childs A (score 1) | Childs B (score 2) | Childs C (score 3) |
|---|---|---|---|
| Serum bilirubin | < 2mg% | 2 - 3mg% | > 3mg% |
| Serum protein | > 3.5 gm% | 2.8 - 3.4 gm% | < 2.8 gm% |
| Ascites | Nil | Mild | Moderate to severe |
| Prothrombin time | < 14 seconds | 15- 17 seconds | > 18 seconds |
| Encephalopathy | Nil | Mild to moderate | Moderate to severe |

In primary biliary cirrhosis and primary sclerosing cholangitis alone the following serum bilirubin values are considered for scoring.

| | Childs A (score 1) | Childs B (score 2) | Childs C (score 3) |
|---|---|---|---|
| Serum bilirubin | < 4mg% | 4 - 10mg% | > 10mg% |

Minimum score of CTP is 5 and maximum score is 15. Based on scoring system, cirrhosis was classified as Childs A when the total score was 5 and 6, Childs B when the total score was 7 to 9 and Childs C when the total score is exceeded 9.

**Details of index and subsequent bleed:** Index bleed was defined as an individual who had a first variceal bleed in his/or her life time. Bleed either early or late following an index bleed was labeled as a subsequent bleed.

For study purpose, a bleeder was defined as one who had registered as a bleeder at the initiation of the study or had a bleed atleast once during the study period.

**Grades of esophageal varices**: It was assessed by using upper endoscopy and **Paquet's grading** for esophageal varices was applied.

1. Grade I: Small varices without luminal prolapse
2. Grade II: Moderate varices with luminal prolapse and minimal obscuring of OG junction.
3. Grade III: Large varices substantially obscuring the OG junction.
4. Grade IV: Very large varices completely obscuring the OG junction.

Varices seen in fundus of the stomach is labeled as fundal varices. It is classified as tortuous type, nodular type and tumouros type.

Presence or absence of red signs such as red wheal sign, cheery red spots were documented , all indicators of an imminent bleed.

**Blood chemistry included:**

**Liver function tests** such as serum bilirubin (direct as well as indirect fraction), aspartate & alanine transaminase, serum total protein including albumin and globulin and prothrombin time, renal function tests. Baseline serum

alphafetoprotein was estimated in all the patients at time of registration and once in every 6-months.

The **management protocol** of the bleeders and non bleeders was based on the grades of varices. Irrespective of grades of varices all bleeders had serial sclerotherapy at three weekly intervals until obliteration of varices in combination with propranolol 20 mg twice a day. Those with fundal varices were on propranolol 40 mg twice a day in combination with isosorbide mononitrate 20 mg once a day. Non bleeders with varices-grades III and IV had primary prophylaxis with propranolol 20 mg twice a day. Due to economic constraints, EVL the current recommended procedure, was not advocated for primary endoscopic prophylaxis.

Individuals were followed up at monthly intervals for variceal bleed, cirrhosis related complications such as spontaneous bacterial peritonitis, hepatorenal syndrome, encephalopathy and hepatoma.

**Statistical analysis**

Demographic and clinical data were expressed as frequency with their percentage. Bi-variate analysis of Pearson's Chi - squared test, Yates corrected Chi – squared test and Fisher's exact test were used for calculating differences in the demographic and clinical data between the variceal bleeders and the non bleeders. Logistic regression multivariate analysis was used to identify the significant risk factors.

## OBSERVATION AND RESULTS

205 of the 223 patients registered until 30th June 2005, fulfilled the criteria and completed the study. 18 patients were lost to follow up and could not be contacted. There were 145 male and 60 female patients. The mean age for men was 44 + 15.1 yrs and for women 43 + 14.3 yrs. There were 95 cirrhotics who had a variceal bleed during the study period and 110 were nonbleeders. The male female ratio in the two groups was 2:1 and 2.9:1 respectively.

Amongst the bleeders, 63 (66.3%) were male and 32 (33.7%) were female. Regarding etiology of cirrhosis, in descending order of frequency, unknown etiology contributed to 43.1%, ethanol to 27.3%, virus related to 24.2% and others 5.2%. Endoscopic esophageal varices Grade I & II and grade III & IV were seen in 38.9% and 61.1% respectively. The frequency of cherry red spots was 5.2% and fundal varices was 18.9%. Diabetes mellitus was co-existing in 9.5% and

essential hypertension in 6.3%. 73.7% belonged to Childs A, 26.3% to Childs B. There were none with Childs C.

Amongst the non bleeders, 89 (80.9%) were male and 21(19.1%) were female. The cause for cirrhosis was, virus related in 44.5%, unknown in 25.5%, ethanol related in 24.5%, and others (5.5%) in descending order of frequency. Endoscopic esophageal varices grade I & II and grade III & IV were 85.5% and 14.5% respectively. The frequency of cherry red spots was present in only one case; five had fundal varices. Co-existing diabetes mellitus was present in 15.5% and hypertension in 4.5%. 29.1% belonged to Childs A, 66.4% to Childs B and 4.5% to Childs C.

Table I summarizes the duration of illness, the etiology, the co-morbid disease states and predictors of variceal bleed in the two groups. An average of six sessions of sclerotherapy (range varies from 4 to 9) downgraded the varices to grade I. One patient with fundal variceal bleed and failed sclerotherapy required emergency devascularisation.

On univariate analysis, age of presentation, gender, established etiological factors and co morbid illness did not influence the risk of a variceal bleed. Unknown etiology (p-0.006), higher grades of varices (III and IV) (p -0.001), presence of cherry red spots (p-0.03), fundal varices (p-0.001) and Childs A CPT score (p

-0.04) had significant influence over the bleed rates.

Multivariate analysis (Table II) showed that patients with lower grade of varices (I & II) had 4 - times lower risk of bleed and the presence of fundal varices placed the patients at a three - fold increased risk. However unknown etiology, cherry red spot and CPT score did not affect the rebleed rates.

Among the bleeders, 70 variceal bleeders presented with an index bleed and all belonged to Childs A; 38 of them progressed to Childs B (54.28%). Subsequent variceal bleed occurred in 27 patients. The mean interval between the first and second variceal bleed in this subgroup was 8 + 7.7 months. 14 patients bled for a third time after a mean interval of 7 + 12.5 months. 13 patients had no further variceal bleed (48.15%). The risk factors that influenced the subsequent bleeds were similar to that of the initial bleed except that the CPT score had now progressed to Childs B. Two deaths occurred due to a variceal bleed: one following surgery and the other due to failed medical and endotherapy; one each succumbed to hepatic encephalopathy, hepatorenal syndrome and hepatoma. Three developed spontaneous bacterial peritonitis.

Twenty-five (18.5%) patients who had not bled at the time of registration, bled for the first time after a mean period of 7 + 8.6 months (range 1 - 15 months) during the 18 month follow up. Two had a second bleed at a mean interval of 5 months.

Comparing index bleeders and bleeders on follow-up, except CPT score there is no significant difference (Table III). Four succumbed to hepatic encephalopathy and two to hepatorenal syndrome. None developed spontaneous bacterial peritonitis or hepatocellular carcinoma.

## DISCUSSION

Esophageal variceal bleed is common in 30% of cirrhotic patients, with a one year mortality of 50% after the initial bleed.[1-6] The greatest risk is during the first 48 to 72 hours and more than 50% of all early rebleed episodes occur within the first 10 days after cessation of active hemorrhage.[7-9]

The present study has prospectively looked into the bleed pattern amongst cirrhotics with portal hypertension in a south Indian population. The statistically significant variables which differentiated a variceal bleeder from a non bleeder during the 18 month follow-up were large sized varices, cherry red spots and fundal varices both for the index bleeders and subsequent bleeders. The results are similar to that reported by other workers (67,68). Kleber et al (69) however, found that CTP score did not influence the bleed rates but did influence the mortality.

A high risk of index bleed has been attributed to continued alcohol use, poor liver function (Child-Pugh Class C) and ascites (69). Alcohol and viruses did not increase the risk of index bleed in the present series, unlike the reports by others (70).

A high incidence of rebleed rate (30–50%) has been documented after endoscopic sclerotherapy (71-73). Attributable factors include age greater than 60 years,

hemoglobin of less than 8 gm/dL, large varices, clot on varices, actively bleeding varices, renal failure and ascites (70,74). The rebleed rate at 18 months in the present series was 29.4% figures similar to North Italian Endoscopic Club multicentric report (NIEC)(75) of 26.5% over a median period of 23 months and other studies (66,67). The risk factors for variceal rebleed in the present series were similar to that of the initial bleed and not much of difference was noted in the interval between the first and second and between second and third bleed, results comparable to the NIEC report.

Survival rates after index bleed without treatment has varied from 32-80% (76,77). Each subsequent bleed is associated with at least a 20% to 30% risk of death (70). Mortality rate in our series was 2% following sclerotherapy; both the patients had two subsequent bleeds. Summarizing, the risk of variceal bleed amongst cirrhotics in our series is directly related to the grades of varices, results similar to that reported in the west. Variceal rebleed rates and bleed related mortality is low in an era of sclerotherapy

## SUMMARY & CONCLUSION

Esophageal variceal bleed pattern in 205 cirrhotics were studied between January 2005 to June 2006.

Age and gender did not influence the bleed pattern amongst bleeders and non bleeders.

Though unknown etiology among bleeders and viral related etiology among non bleeders were common causes for cirrhosis, it was not significant.

Higher grades of varices, presence of cherry red spots and fundal varices were the predictors of variceal bleed in liver cirrhosis.

The risk factors that influenced the subsequent bleeds were similar to that of the initial bleed.

There was no role for co-morbid diseases such as diabetes and hypertension in variceal bleed and bleed related mortality.

Most of index bleeders belonged to Childs A and became Childs B following bleed. Variceal bleed related mortality following endoscopic sclerotherapy was low.

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