STUDIES IN PORTAL HYPERTENSION

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STUDIES IN PORTAL HYPERTENSION

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Voor mijn Moeder en ter nagedachtenis aan mijn Vader

Voor Anneke

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1

GENERAL INTRODUCTION

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INTRODUCTION

The portal venous system and portal hypertension (1-3)

The veins of the portal venous system are unique since, unlike other veins, they do not drain directly into the systemic venous circulation or the heart. In stead, the portal venous system is the main vascular system supplying another organ, the liver. Normal total liver blood flow is approximately 1600 ml/minute; 1200 ml (75%) is delivered by the portal vein and 400 ml by the hepatic artery. The liver receives 25-30% of the cardiac output. Blood flow through the liver is higher than in any other organ and it is understandable that changes in hepatic resistance may have marked circulatory consequences.

The portal system includes all veins that carry blood from the abdominal part of the intestinal tract, the gall bladder, pancreas and spleen. The portal vein is formed by the union of the splenic vein and the superior and inferior mesenteric veins anterior to the head of the pancreas and extends for a distance of 5 - 8 cm to the porta hepatis. There are two main branches while the further intrahepatic distribution is segmental, accompanying the hepatic arterial- and bile duct system. The inferior mesenteric vein usually enters the splenic vein before joining the superior mesenteric vein but may also enter the portal vein at the junction of the splenic and superior mesenteric vein.

Portal hypertension is defined as a sustained increase in pressure in the portal venous system. Portal pressure is the resultant of the volume of blood flowing through the portal venous system and the resistance to that flow. The normal portal pressure is usually expressed as the portal venous pressure gradient, i.e. the absolute pressure in the portal venous system minus the intraabdominal systemic venous pressure, and ranges from 3 to 6 mm Hg (4). The absolute portal pressure can be elevated by ascites, increments in systemic venous pressure and other phenomena. Since any of these factors increase all intraabdominal venous pressures equally, it is essential to use an internal zero reference, e.g. the unwedged hepatic venous pressure or the inferior vena cava pressure, to correct for artificial effects on the portal venous pressure.

Clinically significant portal hypertension, with formation of oesophageal varices, requires the gradient to increase above 10 mm Hg. Variceal bleeding is rarely observed when the portal pressure gradient is less than 12 mm Hg (5, 6). In patients with alcoholic cirrhosis, no relationship was found between the degree of portal hypertension and the risk of gastrointestinal bleeding or the size of oesophageal varices (7). Patients with varices receiving treatment with propranolol become protected against the risk of variceal bleeding when the gradient is lowered to 12 mm Hg or less (8).

Methods for the measurement of portal pressure (3, 9)

Direct methods are transjugular transhepatic or percutaneous transhepatic catheterization of the portal vein, catheterization of a mesenteric vein during abdominal surgery and portal puncture after surgical recanalization of the umbilical vein. Indirect methods are the measurement of the free and wedged hepatic venous pressures at hepatic vein catheterization and splenic pulp puncture. The transjugular pressure measurement is routinely performed during transjugular intrahepatic porto-systemic shunt (TIPS) creation (10). Hepatic vein catheterization may be used for diagnostic purposes, for monitoring the effects of pharmacological therapy and as a prognostic tool (11). Pressure in oesophageal varices can be measured by direct puncture or by using endoscopic pressure-sensitive gauges. Several studies found that variceal pressure is significantly lower than is portal pressure owing to resistance offered by the portosystemic collateral vessels (12). The results obtained with the indirect endoscopic technique have been reported to be reproducible. This non-invasive method may be helpful for prognostic purposes (13) and for monitoring effects of pharmacological treatment of portal hypertension (14), and probably deserves introduction on a larger scale.

Etiology of portal hypertension

The etiology of portal hypertension can be subdivided in left-sided, pre-hepatic, intrahepatic and post-hepatic causes (table 1), according to the site of abnormality leading to portal hypertension.

Left-sided (synonyms: segmental or sinistral) **portal hypertension** (15) (16) is an uncommon, loco-regional form of pre-hepatic portal hypertension involving the splenic venous territory, caused by an obstruction of the splenic vein. The most frequent causes are pancreatic cancer, pancreatic (pseudo)cysts, chronic pancreatitis and aneurysms of the splenic artery. This condition is characterized by the formation of collaterals in the gastric fundal region; oesophageal varices are usually absent. Awareness of this entity is of particular relevance since in patients with variceal bleeding splenectomy is curative.

Table 1. Classification of portal hypertension

type		main causes
left-sided		obstruction of splenic vein due to pancreatic disease
pre-hepatic		portal vein thrombosis
		compression/obstruction of portal vein due to cancer
intrahepatic		
	pre-sinusoidal	schistosomiasis
		(‘early’ cirrhotic stage of) PBC
		congenital hepatic fibrosis
		sarcoidosis
		idiopathic portal hypertension
		nodular regenerative hyperplasia
	sinusoidal	liver cirrhosis
	post-sinusoidal	veno-occlusive disease
		hepatic vein thrombosis
		metastatic tumor
posthepatic		inferior vena cava thrombosis or web
		constrictive pericarditis
		congestive heart failure

Prehepatic portal hypertension is caused by lesions obstructing blood flow or by an excessive inflow into the portal venous system (arterial-portal shunt) before it enters the liver. The prototype is portal vein thrombosis. Pressure is increased in the portal system proximal to the obstruction. Ascites is rare. It is important to realize that the hepatic venous pressure gradient is normal.

Intrahepatic presinusoidal portal hypertension is characterized by abnormalities resulting in an increased resistance at the level of portal venules. The prototype is schistosomiasis. Ascites is rare and the hepatic venous pressure gradient is normal.

Intrahepatic sinusoidal portal hypertension is the commonest type of portal hypertension encountered in the Western world. The prototype is alcoholic cirrhosis. Obstruction at the sinusoidal level is predominant and ascites is common. The hepatic venous pressure gradient is increased.

Intrahepatic postsinusoidal portal hypertension occurs in veno-occlusive disease as seen after bone-marrow transplantation and after ingestion of senechio alkaloids. Other causes include thrombosis of the main hepatic veins (Budd-Chiari syndrome), congenital hepatic venous webs and metastatic tumors. Ascites is a prominent feature. The hepatic venous pressure gradient is elevated.

Posthepatic portal hypertension is caused by abnormalities outside the liver. Ascites is often intractable. Absolute portal pressure is increased but not the hepatic portal venous gradient.

It should be noted that in many hepatic disorders there may be several areas of obstruction, and as the disease progresses new sites may become involved (2). Therefore, hepatic venous pressure measurements may yield results that differ from the typical findings listed here.

Pathophysiology

Increased portal resistance (2, 3)

Normal portal hepatic blood flow is characterized by a low-resistance system: the pressure gradient between the portal venous system and the hepatic venous or systemic venous system, and thus hepatic resistance, is remarkably low. Portal venous blood flow into the portal system is actively regulated by changes in vascular tonus at the level of the splanchnic arterioles and by cardiac output. In the normal liver portal pressure remains low over wide ranges of portal flows.

In most types of portal hypertension, the primary cause of an increase in portal venous pressure is an increased resistance to portal flow. Formerly, it was assumed that in liver diseases increases in portal resistance are attributable to (macro) structural abnormalities, including fibrotic scarring and nodule formation, leading to occlusion and compression of the normal vascular structures. However, in certain disorders, such as in alcohol-induced liver injury, other anatomical changes, including terminal hepatic vein fibrosis and collagen deposition in the perisinusoidal region or space of Disse, have been observed that are likely to contribute to portal hypertension. The transition of the permeable perisinusoidal space to an impermeable collagenous membrane has been described as capillarization. Other mechanisms involved may be hepatocyte enlargement, dropout of hepatocytes resulting in sinusoidal collapse, amyloid deposition and decreased sinusoidal fenestration. There are also data indicating that functional factors may lead to increased vascular tone. In liver disease hepatic lipocytes may acquire contractile characteristics that make them similar to myofibroblasts. They are postulated to play a role in the regulation of perfusion resistance.

These cells may also be the predominant source of collagen synthesis in alcoholic liver disease. More recently, studies have suggested an important role of vasoactive substances produced by endothelial cells such as endothelins, NO and prostacyclins. Finally, the sympathetic nerve system may be involved in the modulation of intrahepatic resistance. Some of the factors potentially leading to increased resistance to blood flow should be regarded as irreversible. However, other factors, e.g. hepatocyte swelling, the production of endothelial vasoactive substances and sympathetic tone, may be reversible or amenable to pharmacological manipulation.

When portal pressure increases, two physiological adaptive mechanisms, the development of portal-systemic collaterals and an increase in portal venous inflow, can be observed.

Portal-systemic collateral circulation (1-3)

Increased portal pressure is the main factor leading to the formation of portal-systemic collaterals. These vessels carry portal blood to the systemic veins and thereby decompress the portal system. Collaterals that are visible on endoscopic examination are usually described as varices but there is no fundamental difference between collaterals and varices, the distinction being a matter of semantics (17). The predilection site is the gastro-esophageal junction where communications between the portal- and systemic venous circulation are present physiologically. Other sites where collaterals may form or develop are the anorectal region, the falciform ligament, the retroperitoneum and where veins of the portal and systemic venous communicate e.g. at the sites of intestinal-abdominal wall adhesions and enterostomies (18). Varices occurring outside the gastro-oesophageal region are known as ectopic varices.

Although the collateral circulation begins as a consequence of portal hypertension, it evolves into an important mediator of the circulatory derangements in its own right. The vascular resistance of the collateral bed, although lower than that of the obstructed portal system, is nevertheless higher than normal portal resistance. The factors that modulate the development of the collateral system and that regulate flow through it are not yet completely understood. Animal studies have suggested that the endothelium derived relaxing factor NO is involved in modulating vascular resistance in the portal collateral system. Other humoral factors including 5-hydroxytryptamine as well as the adrenergic nervous system may also be involved.

Hyperdynamic circulation

The second mechanism that has been demonstrated to be of importance in causing and maintaining portal hypertension is an increase in total portal inflow. This alteration is associated with a hyperdynamic circulatory state, particularly in the presence of advanced liver disease. The clinical manifestations are rapid pulse, warm extremities and low blood pressure. Hemodynamic studies show high cardiac index, low systemic vascular resistance and an expanded blood volume. Increased portal venous inflow is the result of arteriolar vasodilatation in splanchnic organs, which drain into the portal vein. The mechanism is likely to be multifactorial. Several studies have suggested that nitric oxide and other endothelial factors are involved. Also, other vasodilators of splanchnic origin, including glucagon, contribute to increase portal inflow. Increased production and reduced hepatic uptake from liver disease and shunting may increase circulating levels of these substances and decrease sensitivity to endogenous vasoconstrictors such as norepinephrine. Splanchnic vasodilatation is frequently associated with peripheral vasodilatation, which plays a major role in activation of neurohumoral systems, leading to sodium retention, expansion of plasma volume, and the development and accumulation of ascites.

Complications of portal hypertension

Portal hypertension can lead to a large number of physiological derangements and complications (table 2). The pathophysiology of these complications is variable and complex. Large portosystemic collaterals, or varices, can give rise to bleeding and this is one of the most frequent and serious complications of portal hypertension. Other complications seem related primarily to increased sinusoidal pressure (e.g. formation of ascites), diffuse portal vascular congestion and increased blood flow (e.g. portal hypertensive gastropathy), haemodynamic and hormonal alterations (e.g. hepatorenal syndrome; hepatopulmonary syndrome; GAVE) and increased portal-systemic shunting (e.g. hepatic encephalopathy; spontaneous bacterial peritonitis). However, in most conditions multiple pathophysiological pathways seem involved.

Table 2. Complications of portal hypertension

Bleeding from varices
- oesophageal varices
- gastric varices
- ectopic varices
Portal hypertensive gastropathy
Portal hypertensive colopathy
G(astric) A(antral) V(ascular) E(ctasia)
Ascites
Hepatic hydrothorax
Hepatic encephalopathy
Hepatorenal syndrome
Hepatopulmonary syndrome
Pulmonary hypertension
Spontaneous bacteriaemia
Spontaneous bacterial peritonitis

Aim of the studies collected in this thesis

Our work focussed on one of the most frequent and serious complications of portal hypertension i.e. variceal bleeding. In particular, studies were initiated aimed at developing a more effective therapeutic strategy for the primary and secondary prevention of variceal bleeding.

Aspects of primary prevention of variceal bleeding are discussed in Chapters 2, 3 and 4. Primary prevention implies the need to identify patients at risk. Chapter 2 discusses the feasibility of a simple radiological method to detect oesphageal varices and addresses the reliability of this approach in comparison with the more usual endoscopic diagnostic method.

The majority of patients with oesphageal varices will remain free of bleeding. On the other hand, in a proportion of patients variceal haemorrhage will be a fatal event. Therefore, identification of risk factors for variceal bleeding is of paramount importance, in particular with respect to selecting patients for prophylactic therapy. In chapter 3 we report a study assessing the reliability of the NIEC risk score system and report on attempts to further improve its prognostic reliability.

Chapter 4 reports the results of a multicentre randomized controlled trial assessing sclerotherapy as prophylaxis for first variceal bleeding.

Variceal bleeding is a medical emergency associated with significant morbidity and mortality. In patients with active bleeding one of the medical priorities and challenges is to arrest bleeding. The results of a study on the use of thrombin as an endoscopic haemostatic agent are reported in chapter 5.

A number of treatments have been proposed for the secondary prevention of variceal bleeding. Relative new therapeutic options are TIPS and endoscopic band ligation. In chapter 6 we report the results of a randomized controlled clinical trial comparing these treatment modalities, and discuss our results in the context of the cumulative results of comparable studies.

TIPS is an innovative option for managing complications of portal hypertension. Chapter 7 describes the experience obtained with TIPS in the Erasmus Medical Center in patients with variceal bleeding, refractory ascites and other complications of portal hypertension. Shunt obstruction developing over time is the recognized main technical weakness of TIPS. We analyzed risk factors for shunt obstruction and the long-term patency rate of TIPS in a cohort of patients followed according to a strict surveillance protocol; these results are also incorporated in this chapter.

We have always had a main interest in particular sub-groups of patients with variceal bleeding. Bleeding from ectopic varices is rare and literature data other than case reports are equally rare. In chapter 8 we report our experience with 22 patients, observed over an 18-year period. The results of a therapeutic strategy, consisting of an initial local therapy followed by a shunt procedure as second-line treatment when indicated, are presented and discussed.

In our part of the world variceal bleeding in patients with portal vein thrombosis is infrequent and remarkably few studies have evaluated the efficacy of endoscopic therapy and long-term course in Western populations. In chapter 9 a series of consecutive patients with this condition is reported as well as the long-term results obtained with endoscopic sclerotherapy.

Another relatively rare condition is portal biliopathy, an intriguing and unfamiliar complication of portal hypertension in patients with portal vein thrombosis. Chapter 10 summarizes our observations in a series of patients and discusses pathophysiological, diagnostic and therapeutic aspects.

Chapter 11 summarizes and discusses the studies incorporated in this thesis.

Chapter 12 suggests guidelines, based on the results of recent international consensus meetings and own experience, for prophylaxis and treatment of oesophageal and ectopic variceal bleeding.

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OESOPHAGEAL VARICES: HOW RELIABLE IS A BARIUM SWALLOW?

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ABSTRACT

Although barium swallow is a quick and easy method for diagnosing oesophageal varices, there is considerable variation between observers because objective quantitative radiological criteria have so far not been defined. In order to define these criteria, a blind radiological/endoscopic comparative study using endoscopy as the gold standard was retrospectively carried out in 72 patients. A prospective study was then carried out in 47 patients to define the validity of the radiological criteria found by the first study. The results of both studies showed that the length and the width of the mucosal folds representing varices as measured on barium swallow radiographs have a significant relationship with the grade of the varices as determined by endoscopy. We conclude that barium swallow is a quick and reliable method for quantitative assessment of oesophageal varices.

INTRODUCTION

The purpose of the present study was to define a simple and reliable method for routine evaluation and grading of oesophageal varices. Barium swallow radiology and endoscopy are the methods available for the diagnosis of oesophageal varices. Endoscopy (oesophagoscopy) for the assessment of oesophageal varices has been performed more frequently in the last 10-15 years because it is easily available. This development has also been stimulated by the results of studies suggesting endoscopy to be superior to radiological examination (Conn et al, 1961). Although endoscopy is a relatively safe procedure, it is still associated with a small morbidity and mortality (Hart & Classen, 1990). A major disadvantage of endoscopy is that the interpretation is subjective and often based on non-quantitative data. Several studies have been published showing a significant interobserver variation and lack of objectivity in the classification of oesophageal varices (Conn et al, 1961, 1965; Theodossi et al, 1984; Bendtsen et al, 1990). The problems of endoscopic interpretation and grading are further enhanced by the various endoscopic grading systems that are being used (Dagradi, 1972; Oberhammer et al, 1978; Japanese Research Society for Portal Hypertension, 1980; Bendtsen et al, 1990). Another disadvantage of endoscopy is its high cost; a particular problem in the light of the emerging need for annual assessment now that prophylactic treatment for oesophageal varices is becoming available (North Italian Endoscopic Club, 1988; Hayes et al, 1990; Cales et al, 1990). Barium swallow for assessment of oesophageal varices is safe and quick to perform, can easily be repeated and is acceptable to almost all patients. Since no reliable objective radiological criteria have so far been employed for the grading of varices, we decided to carry out a blind retrospective study in order to define objective radiological criteria, using endoscopy as the gold standard. Subsequently a prospective study was carried out to determine the validity of the newly identified criteria.

MATERIALS AND METHODS

Patient groups

First study (training sample). This group consisted of 72 patients (mean age (sd) 45 years (12)) who were scored blindly on barium swallow without any prior information about the results of the endoscopic examinations. All patients were suffering from chronic liver disease of various aetiology and severity, and were not selected with regard to sex or age. The endoscopic examination of the oesophagus took place within three months of the barium swallow. The results of the radiological assessment were compared with the endoscopic findings, and quantitative criteria (see below) for the radiological grading of varices were subsequently defined using the endoscopic grading as the reference method.

Second study (evaluation sample). This group consisted of 47 patients who were studied prospectively, using the radiological method and criteria derived from the first study in order to validate the newly determined criteria. This group also had endoscopy within three months of barium swallow.

Method of barium swallow

A fasting state was not required. No premedication was given. We used a high-density barium sulphate (EZ.HD 250% wt/vol from EZEM Westbury Co., New York) for good coating of the oesophagus mucosa. To enhance filling of the varices, the Müller manoeuvre was used which consists of forced inspiration against a closed glottis. Mucosal relief views were taken 15-20 s after passage of barium bolus, with the oesophagus in a relaxed state. A total of six views were usually taken, all in the horizontal position: prone with head end of the table in 20-30° Trendelenburg as well as supine and both oblique views. Views in double contrast, and filled and overdistended views were avoided since they tend to efface the varices. Gastric varices were occasionally seen, but no attempt was made to measure or classify these as part of this study.

Parameters used for evaluation of barium swallow

Length. The length of the varices was measured on the radiographs in centimetres. The highest level to which the varices in the oesophagus could be visualized was taken as the proximal limit and the level just above the oesophagogastric junction as the distal limit (Figures 1,2).

Width. The maximum width of the mucosal folds representing varices was measured in mm on the radiographs (Figures 1,2). All the measurements were carried out directly on the radiographs and no corrections for magnification were made.

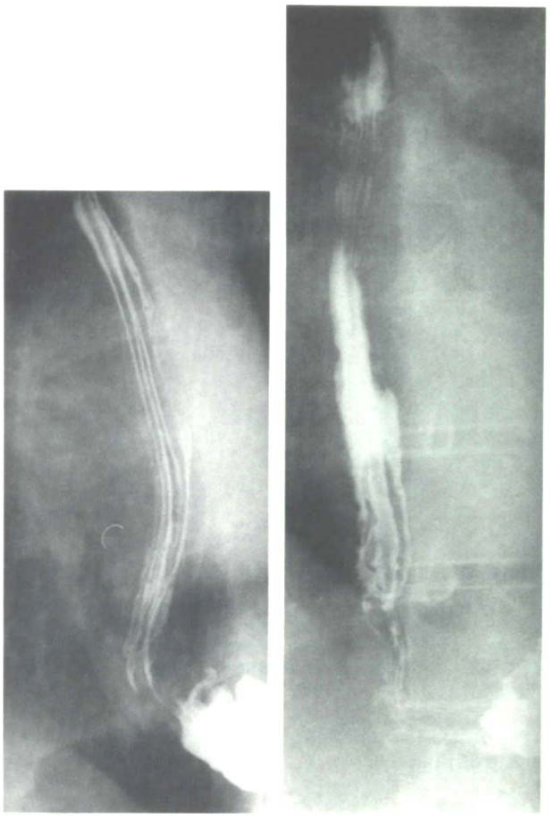

Figure 1: Barium swallow with application of Müller manoeuvre. (a) Parallel folds 2 mm wide in the upper part with some thickened folds and slight turtuosity in the most distal region suggestive of dubious or small varices. (b) A patient with ‘small’ varices (length 6 cm, width 4 mm) in distal oesophagus.

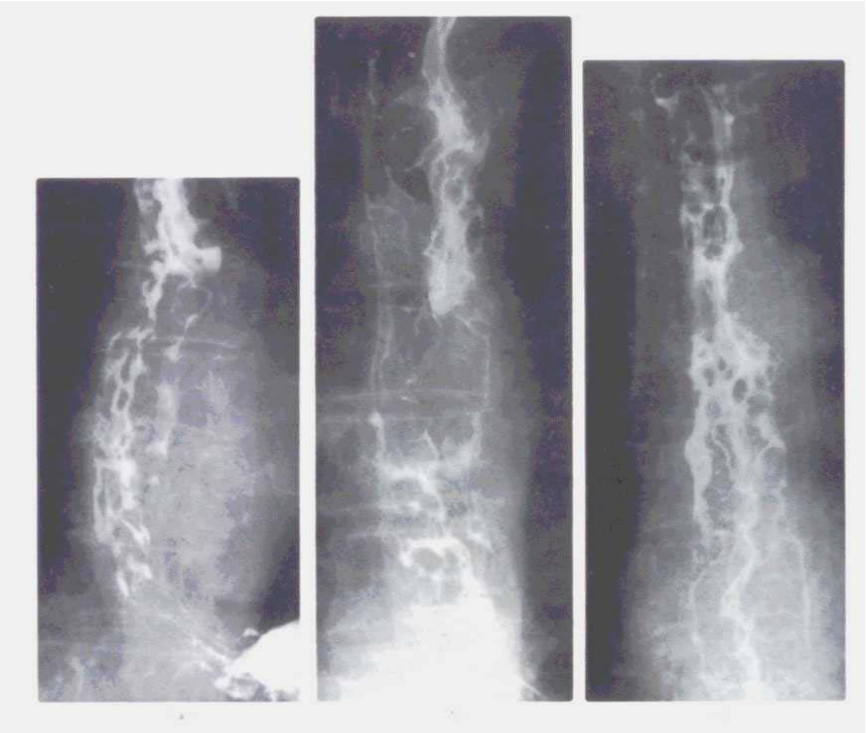

Figure 2: Two patients with 'large' varices with very tortuous folds. (a) Length of varices 22 cm, width 11 mm. (b,c) Length of varices 25 cm, width 15 mm.

Tortuosity. Some degree of subjectivity is impossible to exclude when examining this parameter. The tortuosity of the folds was defined as: no tortuosity (-), slight (+), moderate (+ +) and severe (+ + +) (Figures 1,2).

Endoscopic examination

The patients were investigated by one of four endoscopists, using flexible Olympus® endoscopes. The endoscopist reported the findings in a standardized way, according to Paquet's classification (Oberhammer et al,1972) as follows:

Grade 0: no varices

Grade I: venectasia, disappearing with insufflation

Grade II: larger, clearly visible, usually straight varices, not disappearing with insufflation

Grade III: more prominent varices, locally coil-shaped and partly occupying the lumen

Grade IV: tortuous, sometimes grape-like varices occupying the oesophageal lumen.

Grades 0 and I were grouped together into one group (A) with no varices or small varices and the Grades II, III and IV were grouped together as larger and large varices (B).

Statistical methods

A multivariate logistic regression analysis (Cox, 1970) in the training sample (first study) was used to discriminate between absent or small varices (Grades 0 and I in Group A) and large varices (Grades II, III and IV in Group B). This approach was chosen because from a clinical point of view, the distinction between absent or very small varices and large(r) varices was considered relevant, particularly as the chance of bleeding from varices increases with their size and is virtually nil in Grade I varices. The a priori probability in this analysis was taken as the prevalence of large varices, i.e. 39/72 (54%). The p-values given are two-sided with 0.05 taken as the limit of statistical signficance.

RESULTS

Out of the 72 patients in the first study (training sample), 33 cases had endoscopically absent or small varices (Group A: 19 Grade 0, 14 Grade I), while 39 cases had larger varices (Group B: 11 Grade II, 18 Grade 111, 10 Grade IV). Using multivariate regression it appeared that the length and width of the varices as measured on barium swallow were the most important parameters in discriminating between smaller and larger varices as classified by endoscopy. Although large varices were associated with a greater tortuosity (Mann-Whitney's test: $p < 0.001$) than smaller varices, this parameter did not provide further discriminating power when both the radiological length and width were known. In Figure 3 the length and the width of the varices as assessed by barium swallow are plotted. Open circles represent Group A patients

with varices endoscopically diagnosed as Grades 0 or I, and closed circles, Group B patients with endoscopic Grades II, III or IV varices. Taking a line corresponding to a 50% probability of large varices in the plot of length versus width, (Figure 3), 5 of the 39 cases with large varices were situated below the line. The percentage of false negative outcomes is therefore 13 (5/39). Of the 33 cases with smaller varices, 5 were situated above the line.

The percentage of false positive outcomes is therefore 15 (5/33). The corresponding percentages for sensitivity and specificity were respectively 87% and 85%. In the second study of 47 patients (evaluation sample), 27 cases had no varices or smaller varices on endoscopy (Group A, 17 Grade 0, 10 Grade I) and 20 patients had large varices (Group B, 10 Grade II, 7 Grade 111, 3 Grade IV). The percentages of false positive/negative outcomes obtained in this second group were comparable with those in the first group (Figure 4). The sensitivity and specificity were respectively 80% and 82%.

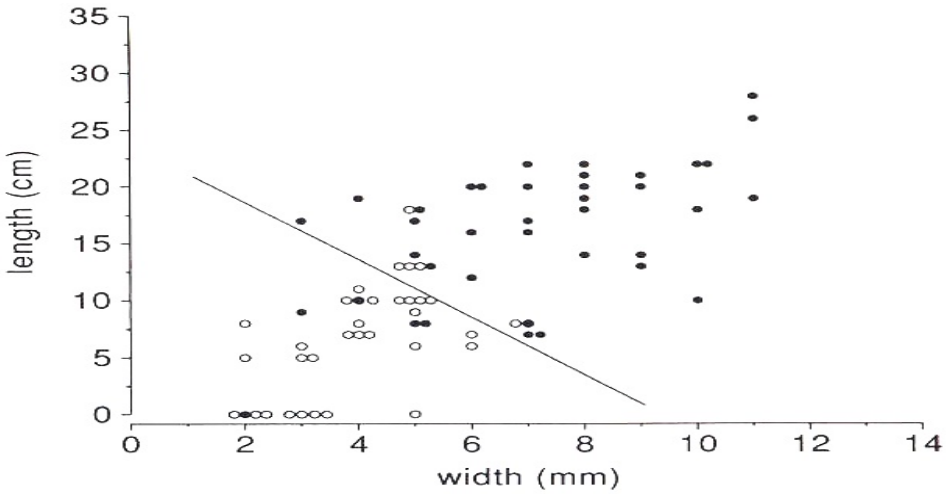

Figure 3: Radiological length vs. width for small or no endoscopic varices (open circles) or medium to large varices (closed circles). The line (length 23.9 – 2.5 x width) corresponds to a 50% chance of larger varices. Total number of patients = 72.

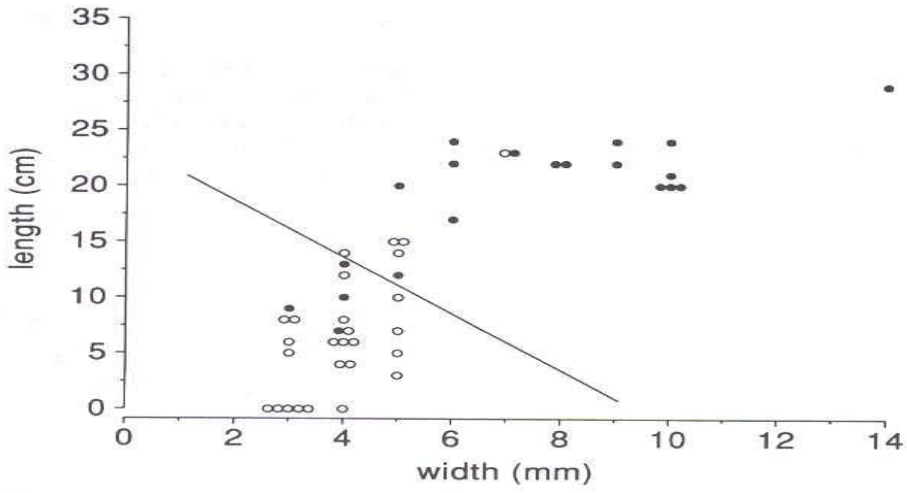

Figure 4: Radiological length vs. width for small or no endoscopic varices (open circles) or medium to large varices (closed circles). The line (length 23.9 – 2.5 x width) corresponds to a 50% chance of larger varices. Total number of patients = 47.

DISCUSSION

Oesophageal varices were first demonstrated radiologically as early as 1928 by Wolf. Schatzki also demonstrated varices in 1931. Bediczka and Taschakert described the classical radiographic appearances of varices in 1932 and their description basically still holds true. The advent of the flexible endoscope and the availability of endoscopic services have led to an increased preference for endoscopy in the last 10-15 years. This, however is not totally based on objective criteria. The major advantage of endoscopy over barium radiology is the ability to local vessel wall abnormalities and colour changes, particularly several types of red spots (Japanese Research Society for Portal Hypertension, 1980). Endoscopy is however invasive and involves a low morbidity and mortality rate (Hart & Classen, 1990). In spite of an endoscopic classification for varices, subjectively still appears to play an important role and leads to significant interobserver variation (Hart & Classen, 1990; Bendtsen et al, 1990). Since it is impossible to enlist any provocative manoeuvres such as Müller or Valsalva in order to enhance the visibility of varices, smaller varices might be missed during endoscopy. Barium swallow, however, is non-invasive, cheaper than endoscopy, and requires no specific preparation or premedication. We did not find that hypotonia of oesophagus achieved by Buscopan injection as used by e.g. Dalinka et al (1972) improved the demonstration of varices and we therefore used no premedication or hypotonic agents during the radiological procedure. Barium swallow is quick to perform and there is virtually no risk of complication. In our experience the procedure was acceptable to all patients. A barium swallow also forms a permanent record of the state of the varices, thus permitting reliable follow-up and multicentre studies. In view of increasing interest in prophylactic treatment of oesophageal varices, barium swallow may be a simple and reliable method for yearly screening as well as for long-term follow-up of patients considered to be at risk of bleeding. The present study was carried out to define objective, quantitative radiological criteria for grading oesophageal varices. The results were compared with routine endoscopic examinations. Using multivariate regression analysis, it appears that the length and width of varices as measured on the radiographs were adequate criteria for discrimination between absent or small (Group A, Grades O and I) varices and larger (Group B, Grades II, III and IV) varices as seen by endoscopy. This was confirmed when the results of the first (retrospective) study were found to be reproduced in the second (prospective) study.

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PROGNOSTIC INDICATORS OF RISK FOR FIRST VARICEAL BLEEDING IN CIRRHOSIS: A MULTICENTER STUDY IN 711 PATIENTS TO VALIDATE AND IMPROVE THE NORTH ITALIAN ENDOSCOPIC CLUB (NIEC) INDEX

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ABSTRACT

Objective: The best known indicator of risk for first bleeding in patients with cirrhosis without previous bleeding is the index devised by the North Italian Endoscopic Club for the Study and Treatment of Esophageal Varices (NIEC index), which results from the combination of size of esophageal varices, severity of red wale marks, and Child-Pugh class. Its efficiency is far from optimal, and validation studies have reported sensitivities and specificities markedly lower than those reported in the original study. In the present study we analyzed the efficiency of NIEC index in a large series of cirrhotic patients with varices without previous bleeding. In addition, we tried to improve the effectiveness of the index by modifying it, and to validate the modifications in an independent group of patients.

Methods: A total of 627 patients were enrolled and followed until either a variceal bleeding or for a maximum of 2 yr. During this time, 117 experienced a first variceal bleeding.

Results: Using Cox's regression analysis, size of varices, severity of red wale marks, and Child-Pugh score were significant and independent predictors of first bleeding, as already noted in the original report of the NIEC group. However, coefficients and standard errors were markedly different, and the importance of size of esophageal varices in the regression was much larger, whereas that of Child-Pugh score was much lower. According to these data, a revised index was developed (Rev-NIEC). Using receiver operating characteristic (ROC) curve analysis, the revised index showed a larger efficiency, and the area under the curve was significantly larger (0.80 ± 0.02 vs 0.74 ± 0.02; $p < 0.01$). In particular, the curve showed that for a specificity of 75%, the new index had a sensitivity of 72% compared to that of 55% of the NIEC index. Validation in an independent sample of 84 patients showed good agreement between predicted and observed risk for bleeding. Validation with the bootstrap technique also showed adequate stability of the results.

Conclusions: The revised index seems to be superior to the traditional index, and may turn out to be more useful in the selection of patients for different therapeutic procedures and in the stratification of patients in clinical trials. (Am J Gastroenterol 2000;95:2915-2920. ©2000 by Am. Coll. of Gastroenterology)

INTRODUCTION

Prediction of the first variceal bleeding in patients with cirrhosis and esophageal varices has been a clinically relevant problem for hepatologists for a long time. Indeed, an accurate prognostic evaluation is the basis for all effective strategies to prevent a first variceal bleeding. Unfortunately, available indicators of risk for bleeding are far from optimal. The most widely used of them is the index of the North Italian Endoscopic Club for the Study and Treatment of Esophageal Varices (NIEC index) (1), which results from the combination of size of esophageal varices, severity of red wale marks, and Child-Pugh class (2). Its prognostic efficiency is rather limited: indeed, when a 78% sensitivity is requested, specificity is only 51 %; conversely, when 88% specificity is requested, sensitivity is only 38% (3). In addition, validation studies in independent samples showed sensitivities and specificities definitely lower than in the original report (4, 5) (Fig. 1). This may be due, at least in part, to the expected decrease in efficiency of all indexes when applied in different samples (6).
For these reasons we aimed to do the following: 1) to assess the efficiency of NIEC index in a large series of cirrhotic patients with varices without previous bleeding; 2) to try to improve the efficiency by deriving possible modifications according to statistical analyses; and 3) to validate the modifications in a further group of patients followed in a different country .

MATERIALS AND METHODS

Clinical, biochemical, and endoscopic data of 627 cirrhotic patients with esophageal varices, without previous variceal bleeding, and without treatment for portal hypertension were collected. All patients were taking part in studies of natural history of portal hypertension, performed in the past years in the Clinica Medica V and Centro di Spleno-Epatologia of the University of Padua (146 patients), the Clinica Medica II of the University of Bologna (326 patients), and the Department of Clinical Medicine and Gastroenterology of the University of Bologna (155 patients). Patients included in Padua had been included in a study of natural history of cirrhotics with varices without previous bleeding (7) or were a subgroup of a series of patients included in a study on the prognostic value of hemodynamic evaluation of portal hypertension (8). Patients followed in the Department of Internal Medicine, Cardioangiology, Hepatology of the University of Bologna were included in a validation study of the Italian Liver Cirrhosis Project on classification of esophageal varices (9); patients followed in the Department of Clinical Medicine and Gastroenterology of the University of Bologna were included in a prospective evaluation of duplex-Doppler ultrasonography in the prediction of variceal hemorrhage (10).

The protocols were approved by the Ethical Committees, and informed consent was obtained from all subjects. The main demographic, clinical, and biochemical data of investigated patients are reported in Table I.

Patients were periodically seen in the outpatient clinics, and were admitted to the hospital when clinically requested; they were considered in the follow-up until a first variceal bleeding, until death, or for up to 2 yr. During this period 119 patients had a variceal bleeding. Bleeding was considered to be arising from varices if a bleeding varix or a fibrin clot was seen at emergency endoscopy or when varices were the only potentially bleeding lesions. In the 18 cases in which emergency endoscopy could not be done, bleeding was considered to be arising from varices, as this is the most frequent source. To validate the NIEC index, it was calculated in individual cases, and a receiver operating characteristic (ROC) curve describing sensitivity and specificity in predicting bleeding for the different values of the NIEC index was built using seven equally spaced cut-off points. Area under the ROC curve (AUC), expression of the overall efficiency of the index in predicting bleeding, was calculated according to Hanley and McNeil (11). The larger the area, the more efficient the index is in predicting bleeding. With the aim of improving prognostic efficiency of NIEC index, possible significant variables related to first variceal bleeding were searched univariately drawing Kaplan-Meier plots (12); variables that turned out to be significant and proportionally spaced with time were tested in a multiple regression model according to Cox (13). In this way a set of significant variables independently linked to the risk for bleeding was obtained, and from them a prognostic index was developed (Rev-NIEC).

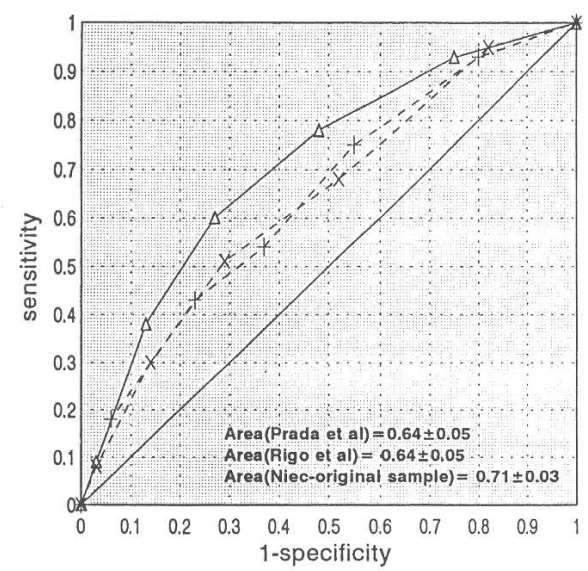

Figure 1. Receiver operating characteristic curve of the prediction of a first variceal bleeding according to the North Italian Endoscopic Club (NIEC) index in the original sample (triangle), and in the validation studies by Prada et al. (ref. 4) (x), and by Rigo et al. (ref. 5) (+).

Table 1. Main Clinical, Biochemical, and Endoscopic Data for the 627 Patients With Cirrhosis

Age (yr)	58 ± 11		
Sex	Male = 311	Female = 317	
Etiology	Alcoholic = 331	Nonalcoholic = 296	
Ascites	Absent = 407	Present = 220	
Hepatic encephalopathy	Absent = 566	Present = 61	
Esophageal varices	F1 = 299	F2 = 229	F3 = 99
Red wale marks	Absent = 288	1 + = 200; 2+ = 115	3+ = 24
Serum albumin (g/dl)	3.46 ± 0.54		
Serum bilirubin (mg/dl)	2.17 ± 2.33		
Prothrombin activity (%)	65 ± 15		
Child-Pugh score	7.4 ± 2.0		
Child-Pugh class	A = 263	B = 259	C = 105

According to this index a ROC curve was built clustering values in seven equally spaced classes. The AUC according to Rev-NIEC was calculated and was compared to the AUC obtained according to the original NIEC index, using the method described for the comparison of AUCs obtained from the same data (14).

To validate Rev-NIEC, a series of 84 patients with varices and without previous variceal bleeding (who were a control group in a clinical trial of sclerotherapy performed at the Division of Internal Medicine, Dijkzigt Hospital, University of Rotterdam, The Netherlands) was considered (15). Patients were comparable for clinical and biochemical characteristics and for observed rate of first variceal bleeding (17 patients in 24 months = 19.5%). In particular, esophageal varices were classified as FI in 35 patients, F2 in 33, and F3 in 16. Red wale marks (RWM) were absent in 46 patients, 1+ in 20, 2+ in 16, and 3+ in two. Child-Pugh class was A in 47 patients, B in 29, and C in eight. Rev-NIEC was calculated in the single patients of the validation group, and a ROC curve describing sensitivity and specificity of the prediction of a first variceal bleeding within 2 yr was built. The AUC for this ROC curve was calculated and was compared to that obtained in the group of 627 patients using the method described to compare AUCs obtained in different groups of patients (11). A further validation was performed according to the boot-strap technique (16). The model was reanalyzed on 20 repeat samples of 313 randomly selected cases of the data set, and the coefficients of variation of the obtained β-coefficients were calculated. This method of internal validation assesses how accurately the model is able to predict the outcome in a new, similar sample of cirrhotic patients. The whole statistical analysis was performed with the BMDP statistical software (Los Angeles, CA) (17).

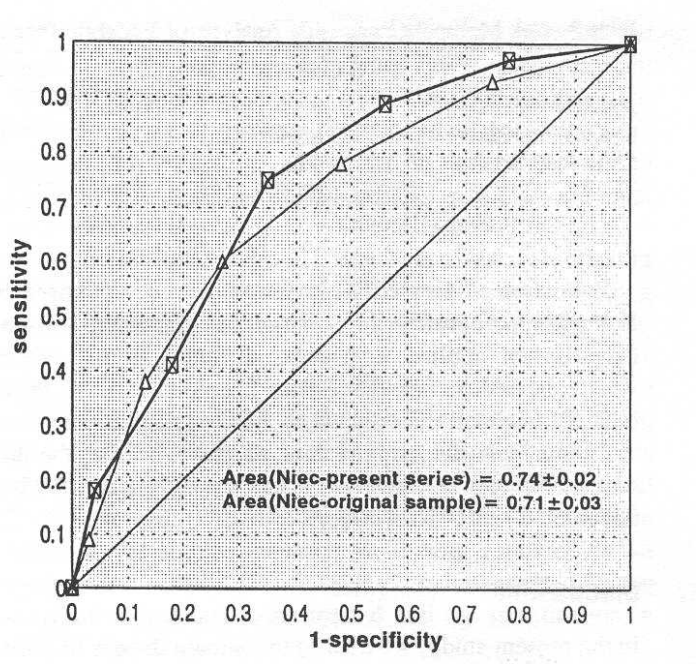

Figure 2. receiver operating characteristics curve of the prediction of a first variceal bleeding according to the North Italian Endoscopic Club (NIEC) index in the original sample (triangle), and in the present series of 627 patients (boxed x]).

RESULTS

Validation of the NIEC Index

The ROC curve built with the present series according to the original NIEC index is shown in Figure 2. Its AUC was not significantly different from that built with the cases reported in the original publication of the NIEC group (1); indeed, it was marginally larger (0.74 ± 0.02 vs 0.71 ± 0.02; p = NS).

Revision of the NIEC Index

On univariate analysis, the probability of variceal bleeding was significantly higher in patients with larger esophageal varices (Mantel-Cox test = 159.8; p = 0.0001), with more severe red wale marks (Mantel-Cox test = 90.9; p = 0.0001), or with more severe liver dysfunction according to the Child-Pugh classification (Mantel-Cox test = 9.9; p = 0.007). According to the multiple regression analysis, the three variables were significant independent predictors of risk for bleeding (Table 2). Considering that the ratios between coefficients and their standard errors represent the relative weight in the regression, it seems that the variceal size is the most important predictor, and that the weight of Child-Pugh score is rather limited. From regression coefficients, a prognostic index (Rev-NIEC) was built according to the formula:

Rev-NIEC = (1.12 X F) + (0.36 X RWM) + (0.04 X Pugh), where F is the size of varices according to the Beppu' s classification (values from 1 to 3), RWM is the severity of RWM (values from 0 to 3), Pugh is the Child-Pugh score (values from 5 to 15). Sensitivities, specificities, and predictive values according to various cut-offs of the two classifications (NIEC and Rev-NIEC) are reported in Table 3.

The ROC curve built from Rev-NIEC values had a significantly higher AUC than that built for the same patients according to the original NIEC index (0.80 ± 0.02 vs 0.74 ± 0.02; z = 5.00; p < 0.01). In particular, for a specificity of 75%, the revised index had a 72% sensitivity compared to the 55% sensitivity of the original index in predicting bleeding (Fig. 3).

Validation of the Revised Index

Internal validation using the bootstap technique gave reasonable stability of the coefficients: indeed, in 20 random samples each containing 50% of the original series, the mean β-coefficients for the three selected variables, calculated according to the Cox regression analysis, were nearly identical to those of the whole series (1.14, 0.36, and 0.08) for size of varices, red wale marks, and Child Pugh score, respectively, and the coefficient of variation was 0.14, 0.34, and 0.35, respectively.

Table 2. Cox Multiple Regression Analysis of Variables Predicting Gastrointestinal Bleeding

Variable value	β-Coefficient	SEM	β -Coefficient/SEM	95% CI for β	Increase in X^2	p
Size of varices (cm)	1.12	0.14	7.53	0.85-1.39	119.3	0.0001
Red wale marks	0.36	0.11	3.40	0.14-0.58	11.4	0.001
Child-Pugh score	0.08	0.04	1.69	0.02-0.150	2.9	0.09

CI = confidence interval; SEM = standard error of the mean.

Validation of Rev-NIEC in the 84 patients followed in Rotterdam demonstrated that prognostic efficiency is maintained when applied to patients different from those in whom the index was developed. Indeed, the ROC curve built with validation cases had an AUC slightly smaller than that built from the original data, as expected; but the difference between the two AUCs was not significant (0.75 ± 0.06 vs 0.80 ± 0.02; z = 0.79; p = NS) (Fig. 4).

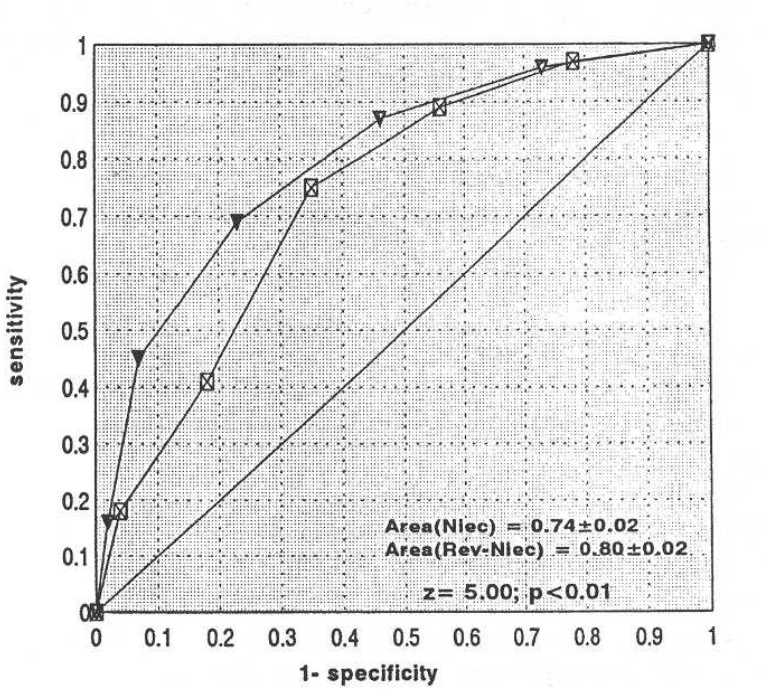

Figure 3. Receiver operating characteristic curve of the prediction of a first variceal bleeding in the present series of 627 patients according to the North Italian Endoscopic Club (NIEC) index (boxed x) and to the revised NIEC index (Rev-NIEC) (inverted triangle).

Table 3. Sensitivity, Specificity, and Predictive Values of the Original and Revised NIEC Classification in Prediction of Bleeding in the 627 Patients

Classification	Sensitivity	Specificity	+Predictive Value	-Predictive Value
NIEC				
>20	0.96	0.22	0.22	0.96
>25	0.89	0.44	0.27	0.94
>30	0.74	0.64	0.33	0.91
>35	0.41	0.82	0.35	0.85
>40	0.18	0.96	0.52	0.83
Rev-NIEC				
>1.75	0.96	0.27	0.24	0.97
>2.50	0.88	0.54	0.31	0.95
>3.25	0.71	0.77	0.42	0.92
>4.00	0.45	0.93	0.60	0.88
>4.75	0.16	0.98	0.66	0.84

NIEC = North Italian Edoscopy Club index; Rev-NIEC = revised NIEC index.

DISCUSSION

In the present study, we tried 1) to validate the use of NIEC index to predict the first variceal bleeding in cirrhosis; 2) to suggest a possible improvement; and 3) to validate the improvement in an independent series of patients. The analysis of the course of the group of 627 patients followed in Padua and Bologna showed that NIEC index is an effective indicator of risk for bleeding. Previous validation studies (4-5) only reported that NIEC index was able to discriminate groups with different outcomes in series different from that in which the index was developed, but a formal statistical validation with ROC curve and AUC comparisons has never been reported. Drawing the ROC curves from the data of the two previous validation studies allowed us to show that in the previous reports the sensibility and specificity was lower than expected (Fig. I). At variance, in our group the index had an adequate performance, keeping the sensitivity and specificity observed in the series in which it was developed. The value of the present observation is reinforced by the fact that our series is larger than the sum of the two other validation studies (4, 5), and that patients were followed in different centers. Despite the good prognostic efficiency of NIEC index observed in the present series, we were able to suggest an improvement of the NIEC index. Indeed, using the Cox regression analysis we confirmed that size of varices, extent of RWM, and severity of liver dysfunction (Child-Pugh classification) are independent predictors of variceal bleeding, as first reported by the NIEC group (I); but a better prognostic efficiency may be obtained modifying the coefficient, and giving a larger weight to size of varices, and less to the Child- Pugh classification. The confidence limits of the β-coefficients in the present regression analysis are rather different from those in the original NIEC report (1) and are not compatible with repeat variability. The relative weight of the various component in the regression equation may be derived from the ratio coefficient to the SE of the coefficient (18). The larger the ratio, the larger the weight of the variable in the overall prediction. In the report of the NIEC group the exact values of the ratios coefficient to SE are not stated, but the points to add in the pocket chart demonstrate that the weight of Child-Pugh class is only marginally smaller than that of variceal size. At variance, in the present series the weight of variceal size was nearly five times that of Child-Pugh score. This implies that, according to the original NIEC index, a patient with FI varices and Child-Pugh class C has approximately the same bleeding risk as that of a patient with F3 varices and Child-Pugh class A, whereas, according to our revised index, the latter has a much higher risk. This modification was associated with a significant change in prognostic efficiency, from 74% to 80%. Such a modification seems reasonable because all prognostic studies agree on the importance of variceal size (8, 10, 19,20), although contrasting evidence is available on the importance of the severity of liver dysfunction in predicting variceal bleeding (21).

The difference in efficiency between the NIEC and the revised indexes is particularly evident in conditions of elevated risk, in which, for a given specificity value (e.g., 75%), sensitivity is increased (e.g., from 55% to 72%; i.e., 17 additional patients for every 100 patients are correctly classified as bleeders within the next 2 yr) (Fig. 3).

A new prognostic indicator usually seems to be excellent in those patients in which it was developed, as the typical pattern of covariates of patients considered in the study are used to define the indicator itself; conversely, it shows a tendency to perform less well in validation studies (6, 22). From these considerations, the need arises to validate all prognostic indexes in different series. In the present study, the validation group collected in The Netherlands had a clinical course very similar to that predicted, and the efficiency of the revised index was confirmed, as the AUCs were not significantly different (Fig. 4). In addition, the internal validation with the bootstrap technique showed steady values for model parameters, confirming the validity and robustness of the model. It might be suggested that the difference between the present model and that underlying NIEC index is only caused by repeat variability, i. e., random variability of the observed series of patients. Nevertheless, the confidence intervals for the coefficients related to variceal size in the regression (coefficient ± 1.96 X SEM, i.e., 0.85-1.39) seem rather far from the value of 0.645 described in the original report of the NIEC group (1), which was never observed in any of the 20 repeated subsamples of the data set containing half of the series, analyzed according to the bootstrap technique.

In conclusion, the NIEC index is an adequate and a validated instrument for predicting first variceal bleeding, but its efficiency may be increased by a modification in the coefficients, giving a larger weight to size of varices and decreasing that of Child-Pugh class. This modification seems to be stable, inasmuch as it was validated in an independent sample. This revised index is suggested for the selection of patients to be treated and for stratification in clinical trials.

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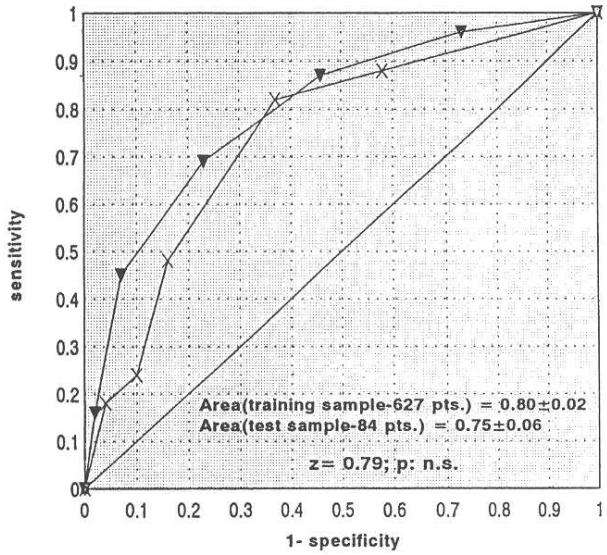

Figure 4. Validation of the revised North Italian Endoscopic Club (NIEC) index: absence of significant difference between receiver operating characteristics curves obtained in the 627 patients of the training sample collected in Padua and Bologna (inverted triangle) and the 84 patients of the test sample collected in Rotterdam (x).

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4

SCLEROTHERAPY FOR THE PRIMARY PREVENTION OF BLEEDING FROM ESOPHAGEAL VARICES. A RANDOMIZED CONTROLLED MULTICENTRE TRIAL

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Submitted

SUMMARY

Background: Since esophageal variceal bleeding is associated with a high mortality rate, prevention of bleeding might be expected to result in improved survival. The first trials to evaluate prophylactic sclerotherapy found a marked beneficial effect of prophylactic treatment. These results, however, were not generally accepted because of methodological aspects and because the reported incidence of bleeding in control subjects was considered unusually high.

Objective: To compare endoscopic sclerotherapy (ES) with a medical regimen for the primary prophylaxis of esophageal variceal bleeding in patients with cirrhosis.

Methods: 166 patients with esophageal varices grade II, III of IV according to Paquet's classification, with evidence of active or progressive liver disease and without prior variceal bleeding, were randomized to groups receiving ES (n=84) or no specific treatment (n=82). Primary end-points were incidence of bleeding and mortality; secondary end-points were complications and costs.

Results: During a mean follow-up of 32 months variceal bleeding occurred in 25% of the patients of the ES group and in 28% of the control group. The incidence of variceal bleeding for the ES and control group was 16% and 16% at 1 year and 33% and 29% at 3 years, respectively. The 1-year survival rate was 87% for the ES group and 84% for the control group; the 3-year survival rate was 62% for each group. In the ES group one death occurred as a direct consequence of variceal bleeding compared to 9 in the other group (p=0.01, log-rank test). Complications were comparable for the two groups. Health care costs for patients assigned to ES were estimated to be higher. Meta-analysis of a large number of trials showed that the effect of prophylactic sclerotherapy is significantly related to the baseline bleeding risk.

Conclusion: In the present trial, prophylactic sclerotherapy did not reduce the incidence of bleeding from varices in patients with liver cirrhosis and a low to moderate bleeding risk. Although sclerotherapy lowered mortality attributable to variceal bleeding, overall survival was not affected. The effect of prophylactic sclerotherapy seems dependent on the underlying bleeding risk. A beneficial effect can only be expected for patients with a high risk for bleeding.

INTRODUCTION

About one-third of patients with liver cirrhosis and varices are likely to undergo hemorrhage during their lifetime (1-5). The average mortality due to the first variceal bleeding has been estimated to be about 30-50% (1, 6, 7). Variceal bleeding therefore represents a frequent cause of death and one might expect survival to improve if bleeding could be prevented.

The potential of primary prevention of variceal bleeding to improve prognosis is dependent on the severity of the underlying disease. There is a close relationship between (risk of) bleeding and degree of liver failure. Often bleeding precipitates or exacerbates liver failure, while deteriorating liver function frequently precedes variceal bleeding. Obviously, prevention of bleeding in end-stage disease is unlikely to affect prognosis. For patients with a relatively preserved liver function, however, prevention of bleeding might improve prognosis, by reducing mortality due to exsanguination as well as from the complications frequently encountered after variceal bleeding, including hepatorenal syndrome, infections and multi-organ failure.

The first type of primary prophylaxis evaluated was the portacaval shunt (3-5). Although shunt surgery reduced the frequency of bleeding, the rate of both mortality and encephalopathy was increased. Data on other prophylactic surgical procedures are limited and do not allow conclusions (8).

The first reports on the use of prophylactic sclerotherapy suggested that this procedure not only significantly reduced the incidence of variceal bleeding (9-12) but also lowered overall mortality (10, 12). However, the results of these trials were disputed, mainly because the reported bleeding risk for control patients in some studies was considered exceptionally high and treatment of acute variceal bleeding episodes was not the same for the two treatment groups (1, 13).

The aim of the present multicentre study was to evaluate the effect of endoscopic sclerotherapy for the primary prevention of variceal bleeding in an adequate number of patients with cirrhosis and esophageal varices, with uniform treatment of variceal bleeding in both groups.

PATIENTS AND METHODS

Patient selection

Eligible patients were adults with endoscopically documented grade II, III or IV esophageal varices (14), absence of prior bleeding from varices, evidence of active and/or progressive liver disease (e.g. as indicated by repeatedly elevated serum transaminases or increasing serum bilirubin levels or development of ascites within the past year) or documented increase in the size of esophageal varices; all patients gave informed consent.

Patients were excluded for the following reasons: malignancy, hemophilia, age older than 70-75 years, no opportunity for follow-up visits.

Centers, study design, randomization and informed consent

This was a multicentre randomized controlled trial that started on 1 May 1986. Patients were included until May 1993 and followed until November 1993. Participating centers (number of patients in parentheses) were the University Hospital Rotterdam (coordinating center)(81); the University Hospital Utrecht (25); the Zuiderziekenhuis, Rotterdam (17); the Academic Medical Center, Amsterdam (15); the Ziekenhuis Leyenburg (12) and Westeinde Hospital (10), The Hague; and the Reinier de Graaf Gasthuis, Delft (6).

Randomization was performed according to Zelen's pre-randomization design (15). After assessment of eligibility, patients were randomized and provided with oral and written information; they were then asked to participate and give informed consent. This procedure was expected to facilitate patient entry, being considered defensible and appropriate taking into account the marked difference between the two treatment options (16). The medical ethical committee of one center did not approve of the pre-randomization method; in this center the conventional procedure was followed.

Treatment was assigned centrally, by telephone contact or by visiting the trial office, using opaque, serially numbered, sealed envelopes. Patients were stratified for center and severity of liver disease according to the Child-Pugh classification (17). Follow-up started at the time of randomization. Patients gave written informed consent. The medical ethical committees of the participating centers approved the trial.

Endoscopic sclerotherapy

Experienced endoscopists performed all procedures using fiber or video-endoscopes. Patients received intravenous sedation consisting of 0.075 – 0.2 mg midazolam/kg. Varices were injected at multiple sites with 0.5-3 ml ethoxysclerol (polidocanol) 1% or 2% (Kreussler, Germany), proceeding upwards from the gastroesophageal junction. The maximum injection volume was 35 ml/session. Patients were hospitalized for the first sclerotherapy session. Successive treatments were planned on an outpatient basis at 3-week intervals until variceal obliteration was achieved. The aim of sclerotherapy was complete variceal eradication. Subsequently control examinations were performed at 6-month intervals. Recurrent varices were treated. When eradication was established on two subsequent visits further control examinations were scheduled at yearly intervals.

Entry and follow-up procedures

Before randomization, all patients underwent upper gastrointestinal endoscopy. Esophageal varices were classified according to Oberhammer and Paquet (14). Meetings of participants were organized to review and standardize diagnostic aspects. The Child-Pugh classification system (17) was used as a measure of functional hepatic reserve. General care of the patients in both groups was identical and involved clinical and biochemical assessment at 3-month intervals.

Definition of key events; management of rebleeding and complications

We used international consensus definitions of variceal bleeding and variceal rebleeding (18). For both groups, the standard therapy for variceal bleeding was resuscitation followed by endoscopic sclerotherapy according to the methods described above, but at intervals of one week until variceal obliteration was achieved. Subsequently, follow-up examinations were performed after 3 months, and then at 6, 9 and finally 12-month intervals. Balloon tamponade was performed when variceal bleeding was not controlled by ES for a period of up to 24 hours and was followed by renewed ES. Therapy for patients with persistent or recurrent variceal bleeding was not defined and decisions were left to the discretion of the individual hospital departments. Variceal obliteration was defined as variceal thrombosis and absence of variceal blood flow as assessed by needle puncture. Variceal eradication was defined as visual absence of variceal columns. Procedure-related mortality was defined as death within 30 days of ES. Esophageal mucosal ulcers after ES were not regarded as a complication unless they caused symptoms, including bleeding and pain.

Analysis of costs

An estimation of the direct medical costs was made by comparing the time spent in the intensive care unit and the ordinary ward, the number of visits to the outpatient department and the number of upper gastrointestinal endoscopies, including sclerotherapy procedures. Only patients admitted to the University Hospital Rotterdam were included. Indirect costs, e.g. economic loss due to inability to work, were not taken into consideration.

Statistics

A sample size calculation was performed assuming a 30% and 10% incidence of bleeding 3 years after entry for the control and ES groups, respectively. To detect this difference with a significance level (alpha) of 0.05 and a power of 90%, and using a two-tailed test, we calculated that we needed to recruit 79 patients for each treatment group. Analyses were performed on an intent-to-treat basis. The primary end-points of this study were variceal bleeding and mortality. Secondary end-points were complications and health-care costs.

Bleeding and mortality were analyzed using the Kaplan-Meier method. Differences between groups were compared by means of the log-rank test. The $\chi 2$ test was used to analyze differences between groups for qualitative data. Paired and unpaired t-tests, or their non-parametric equivalents where appropriate, were used for quantitative data. For analyzing the relationship between baseline bleeding risk and the effect of prophylactic sclerotherapy on the risk of a first variceal bleeding, as reported in the literature and including data of the present trial, the method proposed by Arends et al (19) was used. A two-tailed p-value ≤ 0.05 was considered significant.

RESULTS

Of the 166 patients enrolled in the study 84 were randomized to undergo ES and 82 to the control group (Figure 1). Patient characteristics of the two groups were comparable (table 1). Mean follow-up was 32 ± SD 25 (range 0.1 – 88.5) months; for the ES group 30 ± 23 months and for controls 34 $\pm$ 27 months. Follow-up was incomplete for 11 (ES group 7) patients due to removal, emigration or other reasons. For these cases data were censored at the time of the last visit. In all cases, however, efforts were undertaken to determine whether the patients were alive at the time of analysis and this information, including causes of death, was used for analysis.

Procedures

For sixteen patients assigned to undergo ES, treatment was not instituted because of refusal (n=13), concomitant medical problems (n=2) or miscommunication resulting in failure to initiate ES (n=1). ES was offered to one control patient who repeatedly expressed the explicit wish to be treated because of fear of bleeding. No patient refused to participate in the trial with respect to the prospective recording of follow-up data. During follow-up 9 patients of the control group and 4 of the ES group received a liver transplant. For these cases data were censored at the time of transplantation.

Bleeding

(Table 2) Both the number of patients and the number of episodes of variceal bleeding in the two groups were comparable. The same applied for bleeding due to non-variceal causes. The incidence of bleeding from varices (Figure 2) for the ES and control groups was 16% and 16% at 1 year, 29% and 29% at 3 years and 33% and 35% at 4 years, respectively (NS). Variceal bleeding occurred in 7 of 16 (43%) patients of the ES group who did not receive therapy. For 10/14 patients of the ES group variceal bleeding occurred early (mean 3.5 months, range 1 day - 9 months), before variceal eradication had been achieved. Two of these patients had a variceal bleeding after randomization but before ES was started.

In 4 patients who had ES which resulted in variceal eradication, variceal bleeding occurred after a mean period of 28 months and 5.5 (range 4-9) ES sessions.

The incidence of upper gastrointestinal hemorrhage due to all causes was 22% for the ES group and 25% for the control group after 1 year and 35 and 36 % after 3 years. Per protocol analysis of those patients who underwent the allocated treatment showed that the incidence of variceal hemorrhage for the ES and control group was 17% and 14% after 1 year and 19% and 29% after 3 years, respectively. The 1 and 2 year incidence of upper gastrointestinal hemorrhage due to all causes was 21% and 29% for the ES group and 15% and 36% for the control group, respectively (NS).

Mortality

Twenty-nine (35%) patients of the ES group died and 33 (40%) of the control group (Table 3). In the ES group only 1 death occurred as a direct consequence of variceal bleeding compared to 9 in the other group (p=0.01, log-rank test). The frequency of other causes of death was comparable. The 1-year survival rate was 87% for the ES group and 84% for the control group; the 3-year survival rate was 62% for each group (figure 3). Univariate analysis showed that 3-year survival for Child-Pugh class A, B and C patients was 77%, 45% and 31% (p = 0.05). No relationship was found between mortality and the size of esophageal varices, etiology of liver disease or participating center.

Complications

Clinical events believed to be related to previous sclerotherapy were compared between both treatment groups (Table 4). Although more complications were noted in the ES group, the difference was not significant. One fatal complication occurred in a patient of the ES group due to esophageal perforation after two treatment sessions. Two patients developed symptomatic submucosal esophageal hematomas, and in one case this complication was observed on two occasions. In all cases spontaneous and complete resolution ensued. Two to four endoscopic dilatations were required in 3 cases of esophageal stenosis following sclerotherapy; in all cases the symptoms were alleviated. We found no evidence that the frequency of complications differed between centers. 8 /91 (9%) Child-Pugh class A patients suffered a complication compared to 8/57 (14%) class B patients and 1/18 (6%) class C patients (NS). Thus, no clear relationship was found between the risk of complications and the severity of liver disease.

Costs

In the University Hospital Rotterdam**,** 299 upper gastrointestinal procedures were carried out in 41 patients assigned to receive ES, compared to 89 procedures for the control group (n=40) (p=. 0001). The mean number of days in hospital was 55 for the ES and 35 for the control patients (NS). The total number of days in hospital was 2277 for the ES group and 1400 for the control group (p=0.05). The time spent in intensive care (ES group 58, controls 48) was comparable but ES patients spent significantly more time in other wards (2219 vs. 1352 days). The numbers of visits to the outpatient department (ES group: mean 13.4; total 549; control group: mean 12.8; total 512) were comparable. Altogether, these data indicate that ES was the more expensive strategy, suggesting that the initially higher costs of prophylaxis due to hospital admissions and endoscopic procedures were not compensated by potentially decreased medical consumption over time.

DISCUSSION

In this randomized trial primary prevention of variceal bleeding using endoscopic sclerotherapy did not reduce the bleeding risk for patients with liver cirrhosis and esophageal varices. We found that prophylactic sclerotherapy lowered the risk of fatal variceal bleeding without affecting overall survival. Finally, complications and costs were more marked among patients receiving endoscopic prophylaxis.

Several factors could possibly explain why sclerotherapy was not found to reduce the risk of variceal bleeding in the current trial. We may have failed to detect a real treatment effect, a type II statistical error. Although the sample size of this study seemed adequate, a type II error remains a realistic possibility, in particular because nearly 20% (16/84) of patients did not undergo the assigned sclerotherapy treatment. Since the bleeding risk for this particular subgroup was high, this may have diluted the beneficial effects of endoscopic prophylaxis. Although per protocol analysis showed a trend in favor of this possibility, it was not significant. Another factor that could have obscured benefits of ES is an unexpected low bleeding rate for the control group. However, we found that the 3-year bleeding risk for control patients was very similar to the predicted 30%, and consequently that this factor does not seem of importance. Although this was a randomized trial, one can never guarantee similarity between groups as far as prognostic variables are concerned. Moreover, differences between groups in baseline bleeding risk could be a source of bias. The distribution of variables of prognostic significance in the two groups, particularly Child-Pugh scores, age and variceal size, however, make it unlikely that such a bias was important. Sclerotherapy could increase the initial risk of (variceal) bleeding but have a protective effect over time, eventually translating into an overall treatment benefit.

We found some evidence to support this possibility since the majority of variceal bleeding episodes were observed before achieving variceal eradication, and bleeding after eradication was a rare event. It has been noted previously that the bleeding risk for patients recruited for trials of prophylactic therapy seems highest during the first months of follow-up and decreases to about 1/3 after one year (1, 3). This may suggest that, in retrospect, our sclerotherapy protocol was not optimal and a more intensive regimen, resulting in more rapid eradication of varices (20), could have been more effective.

In this trial ES significantly reduced the mortality rate for variceal bleeding, a finding also reported by other groups (10, 20-24). In only a few studies, however, was this associated with a corresponding improvement in overall survival (10, 20, 21, 24). In these studies variceal bleeding occurred in at least 50% of control patients and was the main cause of death, accounting for 65-80% of mortality. This suggests that the magnitude of the effect of prophylactic sclerotherapy on the risk for variceal bleeding, but also on mortality, is dependent on the baseline bleeding risk. This hypothesis was supported by D'Amico, who found a clear relationship between the effect of sclerotherapy on the incidence of bleeding and the base line bleeding risk as reported in a large number of randomized controlled trials (25). However, the Bayesian statistical method he used (26) was not optimal (19). For analyzing the relationship between baseline risk and treatment effect we therefore used another approach (19). We found, in agreement with D'Amico's results, that a significant ($p<0.001$) relationship exists between the baseline bleeding risk and the effect of treatment when analyzing the results of trials of prophylactic sclerotherapy (Figure 4 and 5), which cannot be attributed to 'regression to the mean'. Thus, endoscopic sclerotherapy is likely to reduce bleeding risk, and probably also mortality, only for patients with a particularly high risk of bleeding. Identification of such patients is possible using the NIEC, or comparable, indices (27, 28). For patients with a low bleeding risk, the effect of sclerotherapy will be marginal or absent; sclerotherapy might even have a deleterious effect. The numerous trials on prophylactic sclerotherapy have been subjected to meta-analysis (29-32). All studies have produced a statistically significant pooled estimate of treatment effect on bleeding risk and mortality in favor of sclerotherapy. Like the results of the individual studies, the conclusions based upon these analyses have been diverse, varying from an undetermined effect of sclerotherapy (30, 31) to sclerotherapy being effective, particularly for high-risk patients (29, 32). One meta-analysis (32) yielded a marked difference in the outcome of trials according to the type of sclerosant used, the results clearly favoring polidocanol.

The general recommendation emerging from international consensus conferences (18, 33, 34) has been that sclerotherapy should not be used for primary prophylaxis of variceal bleeding, mainly because of the statistically significant heterogeneity of the treatment effects as observed in studies, and the availability of a non-invasive and cheap alternative (non selective ß-blocker treatment).

When the trial was designed the possibility existed that, as a result of the pre-randomization method, not all patients would accept the assigned treatment. In practice, refusal proved to be a more frequent problem than expected, which complicated the interpretation of results. However, this problem is not unique to the pre-randomization method and similar difficulties can occur with conventional randomization (3, 5, 35-37). Otherwise, no problems were encountered and our general experience was that the method worked well. Unfortunately, our study design did not allow us to assess whether pre-randomization indeed resulted in increased patient recruitment. Pre-randomization has the potential advantage that, at least in theory, all eligible patients will be selected while the conventional method implies that only a selection of eligible patients will be entered. Consequently, the results of trials using this allocation method may have wider applicability.

The observed rate of complications of sclerotherapy in this study is in agreement with previously reported data. In some studies, however, complications were much more frequent (38, 39). An explanation for these divergent results remains speculative. Variations in technique (32), technical skill and experience with endoscopic sclerotherapy could at least partially account for some of the reported differences.

Our estimation of costs was based on a proportion of patients and the results obviously are preliminary in nature. Nevertheless, our data suggest that prophylactic treatment was the more expensive option. Taking into account the other findings, the cost/benefit ratio of prophylactic sclerotherapy as applied in this study seems unfavorable.

In conclusion, the present results do not support the use of sclerotherapy for primary prevention of variceal bleeding when patients are selected according to the criteria we used. Nevertheless, according to cumulative data from a large number of trials, it can be concluded that endoscopic sclerotherapy can result in a significant decrease in the bleeding risk and, probably, also in bleeding-associated mortality, but only in selected cases with a high bleeding risk. On the basis of lower rates of rebleeding, mortality, complications and the need for fewer endoscopic treatments, variceal band ligation has been shown to be superior to sclerotherapy for secondary prophylaxis of variceal bleeding (40). Several trials have now evaluated band ligation for primary prophylaxis of variceal bleeding. In most, but not all (41), studies band ligation significantly reduced the bleeding risk when compared to control patients (41-43) or administration of propranolol (44), and in one study ligation was also found to improve survival (43).

Additional studies comparing band ligation and non-selective ß -blockers are needed before the role of ligation for primary prevention of variceal bleeding can be defined more precisely. For the time being, ß-blockers remain the principal option for primary prophylaxis of variceal bleeding. For patients with contraindications or intolerance for ß-blockers and for those who are not compliant or do not respond to treatment, variceal band ligation rather than sclerotherapy may be considered for primary prophylaxis (45).

ACKNOWLEDGMENTS

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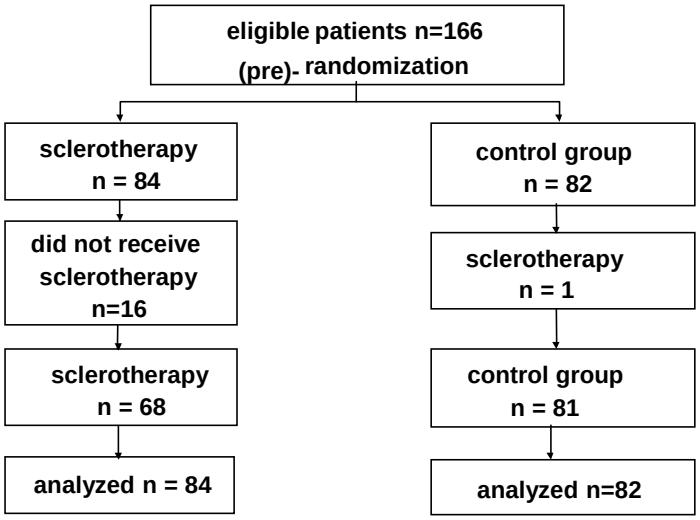

Figure 1

Trial profile

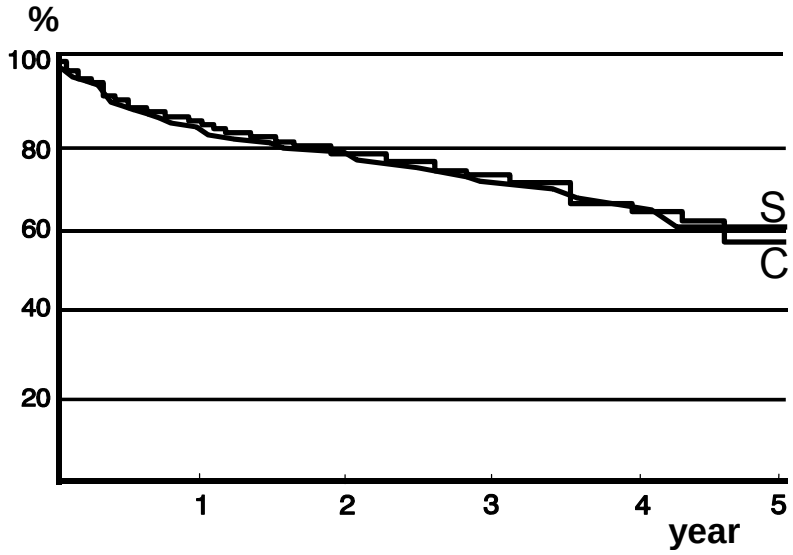

Figure 2

Kaplan-Meier plot showing the percentage of patients free of variceal bleeding (S: sclerotherapy group; C: control group).

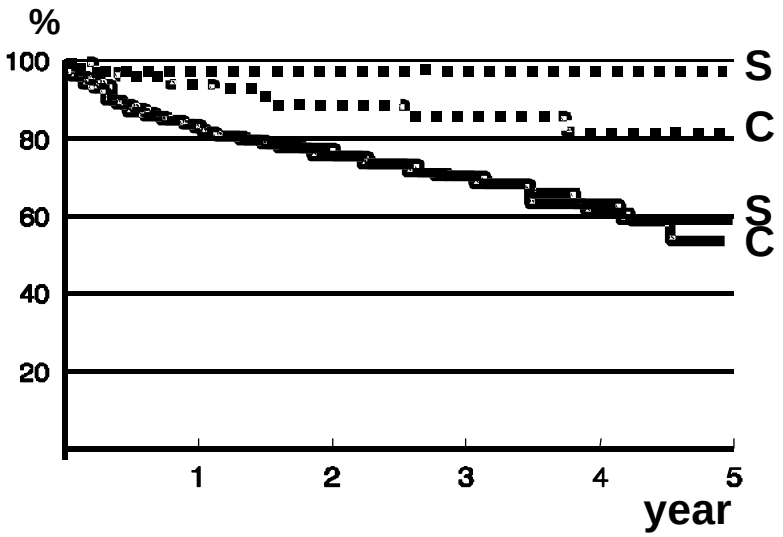

Figure 3

Kaplan-Meier plot showing the percentage of surviving patients (S: sclerotherapy group; C: control group). Overall survival (black lines) was comparable. Mortality due to variceal bleeding (dotted lines) in the sclerotherapy group was significantly lower than in the control group (p=0.01).

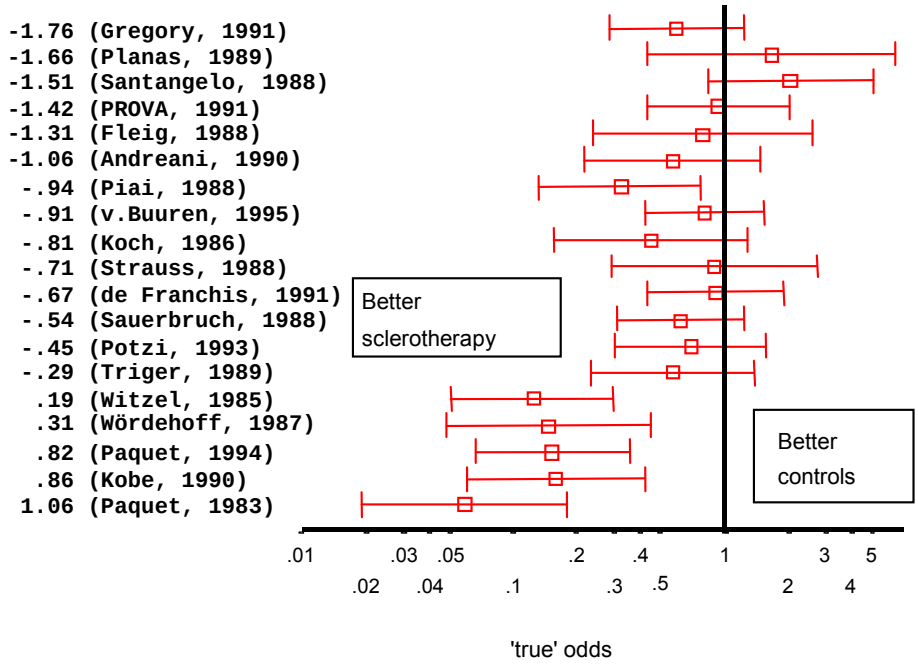

Figure 4

Meta-analysis (19) of the effect of prophylactic sclerotherapy on the incidence of variceal bleeding. The trials are arranged according to the baseline bleeding risk, expressed as the odds after logarithmic transformation for the control groups.

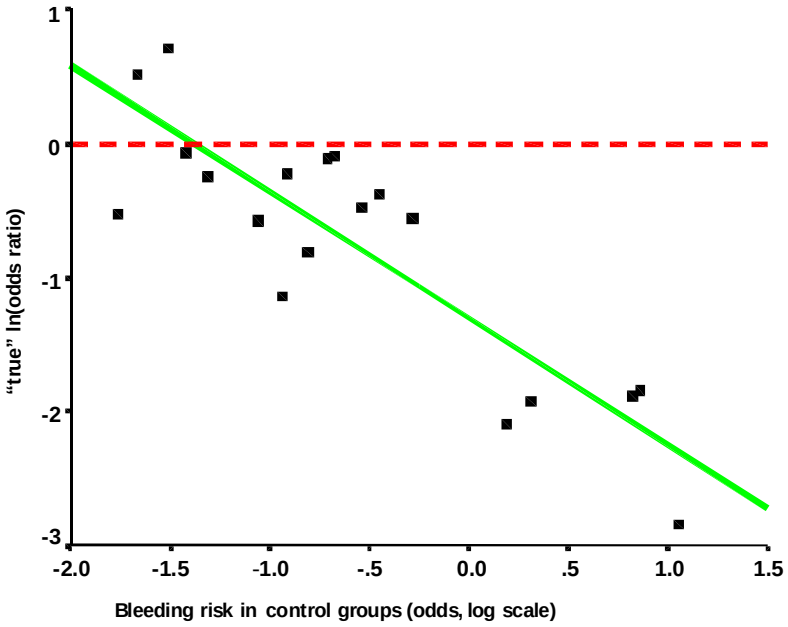

Figure 5

Meta-analysis (19) of the effect of prophylactic sclerotherapy on the incidence of variceal bleeding. Relationship between Odds ratio for bleeding and the baseline bleeding risk.

Table 1. Patient characteristics at entry

Characteristic	Sclerotherapy n=84	Controls n=82
Age	56(23-76)	55(20-72)
Sex (M/F) (n)	46/38	49/33
Diagnosis		
Alcoholic liver disease	41	40
Hepatitis B/C	24	21
PBC/PSC	11	8
Other	24	31
Child-Pugh class A/B/C	52/39/9	57/31/12
Child-Pugh score	6(5-12)	6(5-13)
Esophageal varices		
grade II	47	42
grade III	38	40
grade IV	15	18
Ascites	44	37
Laboratory		
Bilirubin (µmol/l)	27(7-429)	27(7-217)
Albumin (g/l)	36(18-48)	35(23-47)
AT-III (IE/l)	0.7(0.22-1.45)	0.7(0.24-1.32)
ASAT (U/l)	44.5(12-264)	49(12-373)

Results are expressed as percentages and medians with ranges, unless otherwise indicated.
Normal ranges: serum bilirubin <18 µmol/l; albumin > 37 g/l; AT-III 0.85 – 1.50 IE/l; ASAT <35 U/l

Table 2. Variceal bleeding

	Sclerotherapy n = 84	Controls n = 82
Patients		
Variceal bleeding	21 (25%)	23 (28%)
Non-variceal bleeding	7 (8%)	7 (8.5%)
Episodes		
Variceal bleeding	32	39
All upper GI-bleeding	48	49

Table 3. Causes of death

	Sclerotherapy n=84	**Controls** n=82
Variceal bleeding	1	9
Liver failure	9	13
Hepatocellular carcinoma	5	3
Other causes		
Malignancy	2	
Infection	4	3
Stroke	1	3
Bleeding from duodenal ulcer		1
Esophageal perforation[1]	1	
Other causes/unknown	6	1
Total	29	33

[1] complication of sclerotherapy

Table 4. Complications of sclerotherapy

	Sclerotherapy n=84	**Controls** n=82
Esophagus		
Bleeding from ulcerations	2	3
Submucosal esophageal hematoma	2	
Stenosis	2	2
Perforation	1	
Food impaction	1	
Dysphagia		1
Infections		
Bacteremia	1	
Bacterial peritonitis	1	
Pneumonia	1	
Total	11	6

Values are numbers of patients

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5

ENDOSCOPIC INJECTION THERAPY USING THROMBIN: A SAFE AND EFFECTIVE METHOD FOR THE CONTROL OF OESOPHAGOGASTRIC VARICEAL BLEEDING

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SUMMARY

Endoscopic Injection Therapy (EIT) is the treatment of choice for controlling oesophagogastric variceal haemorrhage. There is a need for additional injection fluids with a high thrombogenic potential, as the existing sclerosing agents have a failure rate of 7%-25% in controlling active variceal haemorrhage. The aim of our study was to assess the efficacy and safety of thrombin injections given during 117 EIT sessions to 72 different patients between 1986 and 1991. Results could be evaluated for 107 cases (26 cases with primary active bleeding, 81 cases bleeding from injection sites). Haemostasis was achieved in 103 cases (96.3%). No clinical signs of intravascular coagulation were observed. Doppler-ultrasound examination showed normal portal vein patency in all 26 cases investigated. We conclude that the use of thrombin as a thrombogenic injection fluid during EIT is effective, safe and simple. Thrombin injections may markedly enhance the efficacy of endoscopic treatment for variceal bleeding.

INTRODUCTION

Endoscopic Injection Therapy (EIT) is generally applied as a first line therapy both in controlling haemorrhage from oesophageal (1,2) or gastric (3) varices and in preventing recurrent bleeding. Several sclerosing agents, such as ethanolamin oleate, aethoxysclerol, sodium morrhuate, sodium tetradecyl sulphate and alcohol are in use. Success rates between 75% and 93% for controlling active variceal haemorrhage have been described using one of these regular sclerosing agents (2). This leaves a group of patients who continue to bleed and are in urgent need for further therapy. Another frequent problem of EIT is persistent bleeding from injection sites. Attempts to control this bleeding by injecting more sclerosant may be complicated by subsequent development of deep ulcers, perforations or strictures.

There is an obvious need to enhance the efficacy of EIT by injection fluids with more haemostatic potential.

Soehendra and co-workers were among the first to report on bucrylate injections; they found this method to be effective in stopping active haemorrhage (100% success rate) (4,5).

Since EIT was introduced in our hospital we have used injections of a bovine thrombin solution to control active variceal haemorrhage or persistent bleeding from injection sites whenever haemostasis could not be achieved by injecting regular sclerosants. The objective of the current study was to assess the efficacy and safety of thrombin as a haemostatic injection fluid.

PATIENTS AND METHODS

From October 1986 till July 1991 216 patients underwent 1092 treatment sessions with EIT at our hospital. EIT was employed either to control active variceal haemorrhage and to prevent rebleeding or to prevent a first episode of variceal bleeding in the context of a randomised clinical trial. The endoscopic findings, information on the injection treatment and the results of the therapy were recorded on standard forms. Data for all EIT sessions in which thrombin was used were analysed. The effect of the thrombin was scored as: direct haemostasis, haemostasis within two minutes, haemostasis achieved after two minutes and persistent bleeding. The location of the injection site was scored as: oesophagus, gastric cardia (part of the stomach 4 cm. distal from the oesophagogastric mucosal junction) and gastric fundus (part of the stomach above the plane through the distal border of the gastric cardia, the cardia region not included). In 26 cases (21 patients) Doppler ultrasound investigation was performed within three weeks after EIT to detect possible portal vein thrombosis.

Endoscopy was performed using Olympus GIF IT, Q10 or Q20 endoscopes. Patients received premedication with midazolam 0.075 mg/kg and butylscopolaminebromide 40 mg iv. and atropin 0.5 mg im. Ethanolamin oleate 5% or aethoxysclerol 2% were used as sclerosing agents. Intentionally all injections were given intravariceally in boluses of 0.5-2.0 ml, with a maximum of 40 ml/session.

When bleeding did not readily respond to these injections additional 1 ml boluses of bovine thrombin 1000 NIH-units/ml (Thrombistat®, Warner-Lambert, Amsterdam or Topostatin® Hoffman-LaRoche, Mijdrecht, The Netherlands) were injected intravariceally and this procedure was repeated as often as considered necessary.

RESULTS

During the study period thrombin was administered during 117 EIT sessions to 72 different patients. Twenty-eight (39%) patients received thrombin on more than one occasion (20 patients twice, 8-7 patients 3-7 times). In 2 cases with massive haemorrhage thrombin was used as the primary injection fluid. In 25 cases thrombin was injected after injections with the regular sclerosants had failed to control primary active bleeding. In 84 cases thrombin was injected in an attempt to control haemorrhage, caused by and persisting despite EIT, using one of the regular sclerosing agents. Most thrombin was injected in oesophageal or gastric cardia varices, reflecting the sites where varices and thus bleeds are usually encountered (table 1).

Table 2 shows the haemostatic effect of the thrombin injections. In the 107 evaluable cases in which thrombin was used to control active haemorrhage, haemostasis was achieved 103

times (96.3%). Haemostasis was achieved in all 13 cases where gastric fundus varices were involved. In four cases bleeding continued despite thrombin injections. In one of these cases with primary oesophageal bleeding blood loss became so severe that continuation of EIT was impossible and a Sengtaken tube was introduced. In the other three cases thrombin was injected to control EIT induced haemorrhage (on two occasions in the oesophagus, once in the gastric cardia). Although complete haemostasis could not be achieved, the severity of bleeding decreased markedly. During the study period five patients who suffered from uncontrollable active haemorrhage, did not receive thrombin injections. In four patients EIT could not be applied or continued because the view was too limited; in one patient EIT had to be interrupted because of restlessness.

The mean volume of thrombin injected which resulted in haemostasis was 4.7 ml (SD 2.6, range 1-18). In the four cases in which haemorrhage persisted the mean volume was 9.0 ml (range 6-12).

Our initial fear that heterologous thrombin injections would lead to sensibilization and thus to hypersensitivity reactions on repeated administration could not be substantiated. Almost 40% of all patients received thrombin on more than one occasion but clinically convincing adverse effects were not encountered. One patient suffered from a short period of dyspnoe after the injection of thrombin 4 ml Thrombistat® at his first EIT including thrombin. Another patient suffered a transient blood pressure drop following the thrombin injections (5 ml Thrombistat®, the sixth time this patient received thrombin. Other cases with possible hypersensitivity reactions were not encountered. Doppler-ultrasound to detect subclinical portal thrombosis has been applied after 26 sessions (21 patients) within 21 days of EIT (mean 8.3 days, SD 4.4, range 1-19). No evidence for portal vein thrombosis was found. The mean volume of thrombin injected in these cases was 4.9 ml (SD 2.7, range 1-11). During the in hospital stay no clinical evidence of intravascular coagulation disorders, pulmonary embolism or portal thrombosis was encountered.

DISCUSSION

Our study results show that thrombin injections are effective in both controlling active variceal bleeding and bleeding from injection sites. The results suggest that thrombin, used in addition to sclerosing agents, may improve the efficacy and safety of endoscopic treatment for oesophagogastric variceal bleeding. Thrombin in an attractive injection agent since, in contrast to sclerosants, it exerts immediate thrombogenic activity without accompanying inflammatory or toxic effects. The use of thrombin may minimise the need for repeated injections with sclerosants at the same site and thereby the risk of complications such as (large) ulcers, perforations or oesophageal strictures. In our experience it is rare for active variceal bleeding not to be stoppable with injection therapy if the bleeding point can be

identified; failure to control active bleeding being nearly always due to massive bleeding precluding such identification. Our study further indicates that injections with thrombin are safe, in particular as no clinical or ultrasonic evidence of splanchnic venous thrombosis or pulmonary embolism was encountered. Also, our initial fear for sensibilization and hypersensitivity reactions was not confirmed.

Two other studies have shown that thrombin, used in low dosage and in combination with other sclerosants, can be an useful adjunct to EIT (6,7). Kitano and co-workers carried out a prospective randomised trial in fifty cirrhotic patients with oesophageal varices to examine the effects of human thrombin given concomitantly with ethanolamin oleate (6). They showed a very low rate of active bleeding from the injection sites if thrombin was injected intravariceally before withdrawing the needle, compared to injections with only ethanolamin oleate. Adverse effects of intravasal thrombin injections were not encountered, especially no clinical signs of disseminated intravascular coagulation. After thrombin administration prothrombin- and partial thromboplastin time, fibrinogen and platelet counts showed no significant changes. However, a significant higher level of fibrinogen split products was found following thrombin injections. These results are in accordance with the outcome of an earlier study on the effect of prior administration of thrombin to sodium morrhuate (8).

The injection of (butyl) cyanoacrylate has been described as a very effective technique for arresting bleeding and obliterating large varices (4,5,9,10). Cyanoacrylate hardens within 20-40 seconds under moist conditions and almost immediately in blood. Tissue adhesives must be handled with great care as the injecting needle or even the working channel of the endoscope can become obstructed (4,9,11). Also, systemic emboli to the lungs may occur and two cases of cerebral infarction have been reported (12). A major advantage of thrombin injections is that the administration is relatively simple and requires no specific technical precautions. The additional use of both thrombin and tissue adhesives may be an important technical improvement in endoscopic therapy for variceal bleeding. For severe active bleeding, in particular from gastric varices, tissue adhesive injections may be the preferred technique. Probably, the volume of single injections should not exceed 1 ml. to minimise the risk for systemic dissemination. For less severe bleeding, and for persistent bleeding from injection sites, thrombin injections seem a more attractive therapy.

With the introduction of agents that have immediate obliterative or thrombogenic properties the term ‘endoscopic sclerotherapy’ is not fully adequate. We suggest that ‘endoscopic injection therapy’ may be a more appropriate term.

In conclusion endoscopic injection of thrombin, in addition to conventional sclerosants, is effective, safe and simple and constitutes an important extension of the endoscopic possibilities for treating variceal bleeding.

TABLE 1. Site of thrombin administration

injection site	no. of sessions
1. oesophagus	64 (54.7%)
2. gastric cardia	34 (29.1%)
3. gastric fundus	12 (10.3%)
4. (1+2)	06 (05.1%)
5. (2+3)	01 (00.8%)

TABLE 2. Indications for and effects of thrombin injections for bleeding during endoscopic injection therapy

EFFECT	INDICATION			TOTAL
	thrombin as first agent for variceal bleeding	active bleeding not controlled by conventional sclerosants	bleeding caused by and persisting after conventional EIT	
direct haemostasis	0	12	28	40 (37.4%)
haemostasis < 2 minutes	1	8	43	52 (48.6%)
haemostasis > 2 minutes	1	3	7	11 (10.3%)
persistent bleeding	0	1	3	4 (3.7%)
sessions per indication	2	24	81	107 (100%)

NOTE: Thrombin was used in 117 sessions. In 6 sessions thrombin was used to induce thrombosis in large non-bleeding varices. The effect of thrombin was insufficiently documented in 4 other cases which were excluded from analysis.

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6

TIPS VERSUS VARICEAL BAND LIGATION FOR THE PREVENTION OF REBLEEDING FROM OESOPHAGEAL VARICES. A RANDOMISED CONTROLLED TRIAL

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Submitted

ABSTRACT

Background: First experiences suggested that Transjugular Intrahepatic Portosystemic Shunt (TIPS) is more effective than endoscopic sclerotherapy in the secondary prophylaxis of variceal bleeding but increases the rate of encephalopathy. Variceal band ligation (VBL) has been shown to have significant advantages over sclerotherapy.

Objective: to compare TIPS and VBL in the secondary prophylaxis of oesophageal variceal bleeding in patients with cirrhosis.

Methods: Thirty-seven patients with a first or second episode of variceal bleeding were randomised to undergo TIPS (n=19) or VBL (n=18). Primary end-points were incidence of recurrent bleeding and encephalopathy; secondary end-points were complications and costs.

Results: During a mean follow-up of 21 months 1 episode of recurrent variceal haemorrhage occurred in the TIPS group and 9 episodes in 7 patients in the VBL group. The 2-year incidence of variceal rebleeding was 7% in the TIPS group and 40% in the ligation group (p=0.03). Mortality directly associated with variceal rebleeding was not observed. The incidence of encephalopathy at two years was 55% in the TIPS group and 23% in the VBL group (NS). No difference was found in the frequency of other complications. The two-year survival rate was 61% in the shunted group and 76% in the ligation group (NS). Health care costs for patients assigned to TIPS were estimated to be higher.

Conclusions: TIPS was superior to VBL for the secondary prophylaxis of haemorrhage in patients with cirrhosis and a first or second episode of variceal bleeding. This small study further suggests that TIPS has no marked beneficial effect on survival and is unlikely to be more cost-effective than VBL.

INTRODUCTION

During the last decades of the last century endoscopic sclerotherapy and β-blockers were used as the primary treatments in the secondary prevention of bleeding from varices in patients with cirrhosis. With the introduction of the transjugular intrahepatic portosystemic shunt (TIPS) into clinical practice in 1988, a new and promising therapeutic modality became available for treating patients with this most feared complication of portal hypertension. The first uncontrolled observations indicated superior efficacy with respect to prevention of rebleeding when compared with β-blocker treatment and endoscopic sclerotherapy, and lower procedure related complications and mortality compared with surgical shunts [1, 2]. Recognised disadvantages of TIPS were the increased risk for encephalopathy, a complication inherent to all shunting procedures in portal hypertension, and the high revision rate for shunt dysfunction [3].

Another therapeutic innovation was the introduction of variceal band ligation (VBL). Several comparative trials found VBL to be superior to injection sclerotherapy with regard to the complication rate, the number of treatments sessions and time required to achieve variceal eradication. Ligation resulted in a corresponding reduction of the variceal rebleeding rate and mortality [4].

The aim of the present study was to compare the efficacy, morbidity and costs of treatment with TIPS and VBL in cirrhotic patients with variceal bleeding.

PATIENTS AND METHODS

Patient selection

Eligible patients were men and women aged 18-75 years with a first or second episode of endoscopically proven bleeding from oesophageal varices [5] within two weeks of randomisation, who had not been treated previously with TIPS and provided informed consent. Patients were excluded for the following reasons: prior episodes with hepatic encephalopathy not associated with bleeding, portal vein thrombosis, hepatocellular carcinoma or a prognosis that was considered dismal within two weeks for other reasons, including terminal liver or multiorgan failure.

Centres, study design, randomisation and informed consent

This was a multicentre randomised controlled trial that started 1 September 1995. Patients were included until 1 September 1997 and followed until 31 December 1998. Participating centres were the University Hospital Rotterdam, the Albert Schweitzer Hospital, Dordrecht and the St. Franciscus Hospital, Rotterdam.

Treatment was assigned centrally, by telephone contact or by visiting the trial office, using opaque, serially numbered, sealed envelopes prepared by the trial statistician. The sequence of treatment allocation was computer generated. Patients were stratified for centre, severity of liver disease according to the Child-Pugh classification and previous episodes of variceal bleeding. Randomisation followed as soon as possible after a diagnosis of oesophageal variceal bleeding was established and criteria for inclusion were fulfilled. The assigned treatment was instituted intentionally within 7 days of randomisation. Patients or their next of kin provided written informed consent.

During diagnostic endoscopy band ligation or injection therapy with etoxysclerol or tissue adhesives was allowed to stop active bleeding from varices and to prevent rebleeding. All patients were treated from the time of admission with a 50 µg bolus injection of octreotide followed by intravenous infusion of 50 µg/hour for 48 hours.

The medical ethical committees of the participating centres approved the study.

TIPS

TIPS implantations were performed according to previously described methods [1, 2]. However, in contrast to the policy in most centres, procedures were carried out under general anaesthesia. All patients received intravenous antibiotic prophylaxis (1.5 gram cefuroxim) 30 minutes before the procedure. No routine anticoagulation was given during the procedure or afterwards. Both balloon-expandable (Palmaz stent, Johnson & Johnson) and self-expandable (Wallstent, Schneider, Switzerland) metal stents were used. The gradient between the portal vein pressure and the inferior vena caval pressure was recorded before and after stent insertion. Technical success was defined as a patent stent at the end of the procedure and a portal pressure gradient below 12 mmHg. If contrast injection revealed persistent significant collateral blood flow additional embolisation using micro coils was performed.

Endoscopic band ligation

Experienced endoscopists performed all endoscopic procedures. Varices were ligated using end-viewing endoscopes and a multi-shooter banding device (Speedband®; Boston Scientific Corporation, Natick, USA) according to previously described methods [6, 7]. The ligation was started at the oesophagogastric junction and extended upwards in a spiral fashion, usually until 5-7 cm above the junction. Eradication was defined as disappearance of variceal columns or inability to perform further ligation because variceal tissue could no longer be ‘sucked’ into the ligation device.

Follow-up treatment

Care of the patients in both groups was identical and involved clinical and biochemical assessment at 1 month and 3-monthly intervals thereafter.

For the VBL group treatment was repeated at weekly intervals until obliteration, and then at 3 and 6 monthly intervals. Any persistent or recurrent varices were retreated. When variceal eradication had been documented on two successive 6 monthly visits, control examinations were scheduled at yearly intervals.

For the TIPS group shunt function was assessed using Doppler-ultrasonography at 2, 7 and 30 days after insertion of the shunt and subsequently at 3 monthly intervals. Repeat portography and pressure measurements, under local anaesthesia and mild intravenous sedation with midazolam, were performed at 1 month and 6 months after TIPS and when ultrasonography suggested shunt insufficiency. Shunt insufficiency was treated with balloon dilatation or the insertion of additional stents.

Definition of key events; management of rebleeding and complications

We used international consensus definitions for the acute bleeding episode, (significant) rebleeding and failure to control bleeding [8]. Rebleeding was defined as the occurrence of new haematemesis or melaena after a period of 24 hours or from the 24 hours point of stable vital signs and Hct/Hb following an episode of acute bleeding. The acute bleeding episode is represented by an interval of 48 hours from time of admission (time zero) with no evidence of clinically significant bleeding between 24 and 48 hours. Significant rebleeding was defined as a transfusion requirement of 2 units of blood or more within 24 hours of time zero, together with a systolic blood pressure < 100 mmHg or a postural change of > 20 mmHg and/or pulse rate >100/minute. Rebleeding was specified in terms of total rebleeding, variceal rebleeding and bleeding from other causes. For patients with rebleeding treatment consisted of renewed infusion of octreotide during 2 days, urgent (therapeutic) endoscopy and temporarily balloon tamponade when indicated. For the TIPS group this was followed by portography, measurement of the portal pressure gradient and measures to restore or improve shunt function. Treatment failure, and thereby an indication for other therapy, was defined as the occurrence of two episodes of recurrent variceal bleeding requiring transfusion of 2 units of red blood cells per episode, or the occurrence of three episodes of recurrent variceal bleeding and transfusion of 2 units of red blood cells on at least one occasion. When TIPS creation was unsuccessful patients were further managed by VBL. When VBL failed the choice with respect to further treatment was left to the team taking care for the patient; TIPS or a surgical shunt were proposed as the main treatment options in that situation. Shunt insufficiency, or dysfunction, was defined as a hepatic portal venous pressure gradient over 12 mmHg or angiographic documentation of shunt stenosis or occlusion. Hepatic encephalopathy was assessed by clinical criteria [9]. All episodes were taken into account, irrespective of the presence of possible precipitating factors. Both groups received lactulose to prevent hepatic encephalopathy. The standard dose was 30 ml twice daily and was adjusted to produce two soft stools daily. Hepatic encephalopathy in both groups was treated with increased doses of lactulose and /or temporarily lactulose enemas, and correction of potentially precipitating factors including infections, electrolyte disorders and use of sedatives. If necessary, dietary protein was restricted and additional treatment with antibiotics was instituted.

Analysis of costs

We performed an analysis of the direct medical costs i.e. costs of the time spent in the intensive care unit and on the ordinary ward, and those associated with radiological and endoscopic procedures and administration of blood products. Only patients admitted to the University hospital Rotterdam were included. Indirect costs, e.g. economic loss related to inability to work, were not taken into consideration. Because of the limited number of patients

in this study and the high costs associated with (evaluation for and performance of) liver transplantation, candidate patients for this procedure were excluded from analysis. The mean cumulative costs per patient for both treatment groups were compared.

Statistics

A sample size calculation was performed assuming 20% and 55% rebleeding rates at one year after TIPS and VBL. To detect this difference with a significance threshold alpha of 0.05 and a power of 80%, and using the two-tailed test Fisher exact test, we calculated that we needed to recruit 35 patients in each treatment group within a period of 2 years. Analyses were performed on an intention to treat basis. The primary end-points in this study were variceal rebleeding and hepatic encephalopathy. Secondary end-points were complications and health-care costs.

Rebleeding and mortality were analysed using the Kaplan-Meier method. Differences between groups were compared with the log-rank test. The Chi-2 test was used to analyse differences between groups for qualitative data and paired and unpaired t-tests or their non-parametric equivalents, where appropriate, for quantitative data. A p-value < 0.05 was considered significant.

RESULTS

Entry of patients into the study was much lower than expected. After 2 years, 37 patients were enrolled into the study and it was decided to stop recruitment. Nineteen patients were randomised to TIPS and 18 to VBL (figure 1). We excluded 51 patients for the following reasons: variceal bleeding more than 2 weeks before randomisation (n = 8), refusal (n = 6), hepatocellular carcinoma (n = 7), terminal liver failure (n = 11), performance of emergency TIPS for uncontrolled bleeding before randomisation (n = 4), portal vein thrombosis (n = 6), death before randomisation (n = 2) and other reasons (n = 7) including inability for follow-up or more than two previous variceal bleeding episodes. Patient characteristics were comparable for both groups (table 1). Mean follow-up for the total group was 20.9 months (range 0.6 - 40); for the shunt group 18.4 $\pm$ 12 months and for the VBL group 23.5 $\pm$ 11 months. Mean time from initial diagnostic endoscopy to TIPS was 11.5 $\pm$ 6 days and to VBL 8.7 $\pm$ 7 days. Mean time from randomisation to TIPS was 5.7 $\pm$ 5 days and to VBL 3.9 $\pm$ 3 days (p=0.2).

The number of therapeutic endoscopic procedures in the time between admission and institution of the allocated treatment was comparable for both groups. In the TIPS and VBL group 5 and 3 patients, respectively, had not been treated endoscopically before the allocated treatment was instituted while 11 and 13 patients from the respective groups had one endoscopic treatment. The remaining patients had three or four endoscopic treatments.

Procedures: TIPS implantation failed in one case due to inability to puncture the portal vein and in another case only succeeded at a second attempt. The latter patient developed subtotal portal vein thrombosis and, despite anticoagulation, subsequent complete thrombosis. Both patients were managed by VBL. During the initial TIPS procedure, coil embolisation of portosystemic collaterals was performed in 8 patients. Following TIPS insertion, embolisation was performed after 3 and 6 days in 2 other patients undergoing portography for shunt insufficiency.

All patients in the VBL group received this therapy and none of them required TIPS or another therapy for uncontrolled variceal bleeding later on. In the VBL group eradication of varices was achieved in 14/18 patients after a mean interval of 6 months. Four of these patients rebled from recurrent varices on further follow-up. Despite repeated ligation treatment complete eradication was not achieved in 4 cases.

During the trial 1 patient in the TIPS group and 2 in the VBL group received a liver transplant.

Rebleeding: (Table 2) Rebleeding was observed in 1 patient assigned to TIPS. This was in the single patient in whom placement failed and who subsequently was managed by VBL. The incidence of rebleeding from varices (figure 2) for the TIPS and VBL groups was 7% and 32% at 1 year and 7% and 40% at 2 years, respectively ($p = 0.03$). The incidence of significant variceal rebleeding after 1 and 2 years was 7% for the TIPS group and 12% for the VBL group (NS). (When the 2 patients in whom TIPS placement was unsuccessful were analysed as being randomised to VBL, the difference remained non-significant).

Mortality: Nine patients (47%) patients died in the TIPS group and 4 patients (22%) in the VBL group. There were no deaths attributable to variceal bleeding (table 3). The 1-year survival rate was 68% in the TIPS group and 76% in the VBL group; the 2-year survival rate was 61% and 76%, respectively (figure 3). These differences were not significant. Analysis of subgroups with Child-Pugh classes A, B or C showed no significant differences.

Encephalopathy: At the time of randomisation hepatic encephalopathy was diagnosed in 6 patients. One patient in the TIPS group had grade grade I encephalopathy, improved with therapy and had no recurrence after TIPS. In 5 cases assigned to VBL with grade I (n=3), II (n=1) and III (n=1) encephalopathy, symptoms responded to treatment but recurred in 3. Encephalopathy was a chronic recurrent problem in the 2 patients with grade II/III. Following TIPS de novo encephalopathy developed in 9 (50%) patients, mainly during the first three months. In the VBL group encephalopathy was observed in 4 patients. Two patients in the TIPS group and 3 in the VBL group required rehospitalization for encephalopathy. The 1 and 2 year incidence of encephalopathy was 43% and 55% following TIPS and 23%/23% for the VBL group ($p = 0.13$, log-rank test) (figure 4). One patient treated with TIPS and 2 treated with VBL had recurrent episodes of encephalopathy; these were Child-Pugh class C patients who died of liver failure during follow-up.

Complications: In the TIPS group three treatment related complications were observed: transient haemolytic anaemia, portal vein thrombosis and fatal haemorrhagic stroke in a 73-year old female, occurring immediately after portography and introduction of a second stent for shunt insufficiency. In the VBL group 3 patients had complications: bleeding from therapy related oesophageal ulcers in 2 and gastric perforation after band ligation of the cardiac region in one. The latter patient required laparotomy, with a subsequent favourable course.

Shunt surveillance and function: Two patients did not undergo surveillance portography due to early death. Repeat portography was performed on 24 occasions in 15 of the 17 patients who had successfully inserted shunts. Twelve of these 17 patients (71%) developed shunt insufficiency, with complete occlusion in 4 and shunt stenosis in 8. Eight balloon angioplasties were undertaken in 8 patients on 10 occasions; in 7 patients additional coaxial stents were inserted. Both balloon angioplasty and additional stent insertion for shunt insufficiency were performed in 3 cases. Shunt insufficiency was not accompanied by rebleeding in any of our patients.

Costs: During the first month, the mean costs per patient in the TIPS group were € 10909 and for the VBL group €6818. This difference was caused by higher costs for procedures in the TIPS group (€6657) as compared to the VBL group (€2524). The costs of in-hospital treatment for both groups were comparable. After two years, the mean cumulative costs per patient in the TIPS and VBL groups were €21818 and €15909, respectively. Thus, the initial difference between both groups became more marked over time and was not reduced by potentially decreased medical consumption of TIPS treated patients because they suffered less rebleeding or required less rehospitalization.

DISCUSSION

The results of this randomised trial suggest that TIPS is more effective in preventing variceal rebleeding in patients with liver cirrhosis and a first or second episode of haemorrhage from oesophageal varices compared to VBL. We were unable to demonstrate an advantage of TIPS over VBL with respect to variceal rebleeding defined as significant. Our findings further suggest that the lower incidence of rebleeding obtained with TIPS does not translate into a survival benefit. Finally, TIPS seemed to increase the risk for hepatic encephalopathy.

The obvious major weakness of the present study is its low power, due to our inability to enter more patients into the trial. Thus, this trial may easily have failed to detect real treatment effects (type II error), but may also suggest treatment effects that are non-existent (type I error). Therefore, all results should be interpreted cautiously and clearly this trial does not allow drawing conclusions as to the superiority of one treatment modality over the other. Nevertheless, we consider it important to report our findings in order to add to the available literature data on therapeutic options in variceal bleeding. Particularly, the data reported here

may be used in meta-analyses and thereby increase the reliability of the results of such studies.

In this study, TIPS provided full protection against renewed haemorrhage from varices in those patients who had technically successfully created shunts and remained free from early occlusion due to thrombosis. This applied to 89% of patients intentionally treated with TIPS. Surprisingly, although shunt insufficiency developing over time was not uncommon, in this small series this was not associated with variceal rebleeding, an observation similar to that of Jalan et al. [10]. In contrast, considering the observed 40% risk of rebleeding within two years following VBL, this study confirms that VBL is a relative ineffective procedure in the secondary prophylaxis of variceal haemorrhage. A therapeutic strategy aimed at increasing the efficacy of endoscopic therapy by additional treatment with β-blockers was not shown to lead to improved results in recent studies [11, 12].

The superiority of TIPS in the prevention of variceal rebleeding as compared to endoscopic therapy has now been demonstrated in a number of randomised trials [10-17] and confirmed by meta-analyses [18, 19]. There are no apparent differences in the outcomes regarding the use of sclerotherapy or band ligation [10, 17]. The available data indicate that TIPS creation results in a parallel reduction in the mortality rate due to rebleeding. This result was not statistically significant in a recent meta-analysis comprising the data of 6 trials published as full reports [19]. Re-analysis of these data combined with those of two recently fully reported trials [16, 17] and the present trial shows that 9/326 (3%) of patients died of variceal rebleeding after TIPS and 30/328 (9%) of patients treated endoscopically, a statistically significant difference (Mantel – Haenszel method: p=0.01; Odds ratio 3.4; 95% CI 1.6-7.4; test for homogeneity p=0.02). This difference may be an underestimation of the advantage of TIPS because treatment crossover to ‘salvage’ TIPS was reported for almost 20% of patients randomised to endoscopic therapy in the case of treatment failure.

Mortality was not an end-point in this study. No differences between the TIPS and VBL groups were established, a finding in accordance with most studies. Analysis of total mortality, as reported in 10 trials [10-17] [20] including the present trial, shows that 97/350 shunted patients died versus 85/353 patients treated endoscopically (p= 0.3; Odds ratio 0.8; 95% CI 0.6-1.2; test for homogeneity p=0.7). Several factors may explain why TIPS, despite being more effective in terms of prevention of (mortality due to) rebleeding, fails to improve overall survival. As already discussed, in most studies patients assigned to endoscopic therapy were allowed to crossover to shunt implantation when they failed therapy. This may have obscured a treatment benefit of TIPS. Also, TIPS may be associated with more (fatal) procedure-related complications. In the present study, one death due to stroke seemed related to TIPS creation while other fatal complications, including haemoperitoneum [12] [17, 20] and respiratory depression caused by sedation [10] have been reported. On the whole, however, the occurrence of fatal and non-fatal complications seems comparable for

radiological shunts and endoscopic therapy. Further, in analogy with surgically constructed shunts [21, 22], TIPS may have an adverse effect on liver function, resulting in higher mortality from liver failure. However, the combined data of 9 trials [10-13] [15] [20] [16, 17], including the present report, indicate that 26/326 (11%) shunted patients died of liver failure, compared to 27/328 (8%) endoscopically treated patients, a non-significant difference (Odds ratio 0.7; 95% CI 0.4-1.3; test for homogeneity p=0.8). Fatal infectious disease was observed more frequently after TIPS (TIPS 4.6% vs. endoscopic therapy 2.7 %), but this difference is not significant (Odds ratio 0.6; 95% CI 0.2-1.4; test for homogeneity p=0.8). No clear differences between both treatment options are apparent with respect to other causes of death. For the time being, it is difficult to find a satisfactory explanation for the unaltered mortality risk after TIPS. Possible factors involved are the treatment crossover phenomenon and the presence of a type II statistical error.

Similar to most studies we found that TIPS creation is associated with a higher risk for hepatic encephalopathy. Usually this was a transient problem, readily responding to appropriate therapy. The serious problem of chronic or recurrent encephalopathy was comparable for both treatment groups.

Data on the relative costs of TIPS and endoscopic therapy are particularly scarce and literature data do not allow firm conclusions [18]. Several studies found no difference with respect to the rehospitalization rate [17, 20] [16] or costs [14]. However, this has not been a uniform finding and both higher [23] and lower [10] costs associated with TIPS have been reported. Due to the small sample size, our estimation of costs clearly has a preliminary character, but suggests that costs of TIPS implantation are higher than those of endoscopic therapy. It remains to be established whether the cost benefit ratio of TIPS may change over time, as TIPS may potentially have a beneficial effect on costs related to other complications of portal hypertension, such as ascites and ectopic variceal bleeding, while the reintervention rate over time may gradually decrease [24]. On the other hand, TIPS could also have an opposite effect through a negative effect on liver function.

In conclusion, TIPS compared with endoscopic therapy is more effective in preventing rebleeding from varices. The currently available cumulative data suggest that this results in a reduction of bleeding associated mortality. However, TIPS has not been shown to improve overall survival. The reasons for this failure await further elucidation. TIPS creation increases the risk for hepatic encephalopathy, however this condition usually does not represent a major clinical problem. Further studies should concentrate on the question whether TIPS may be more effective in particular sub-groups, e.g. patients with pre-existent ascites, gastric varices, severe, life-threatening haemorrhage or recurrent haemorrhage despite previous endoscopic therapy. It seems attractive to assess these issues in meta-analyses by combining individual patient data of the available trials. Also, future studies should evaluate whether new types of stents [25, 26] give less rise to shunt insufficiency. If so, TIPS could

further decrease the rebleeding rate from varices, with a parallel decrease in the costs of surveillance. Despite being relative ineffective in preventing recurrent bleeding from varices, and despite other drawbacks such as the necessity of repeated invasive treatment and continued surveillance, endoscopic treatment is likely to remain the main treatment option in most centres until clearly superior alternatives have been identified.

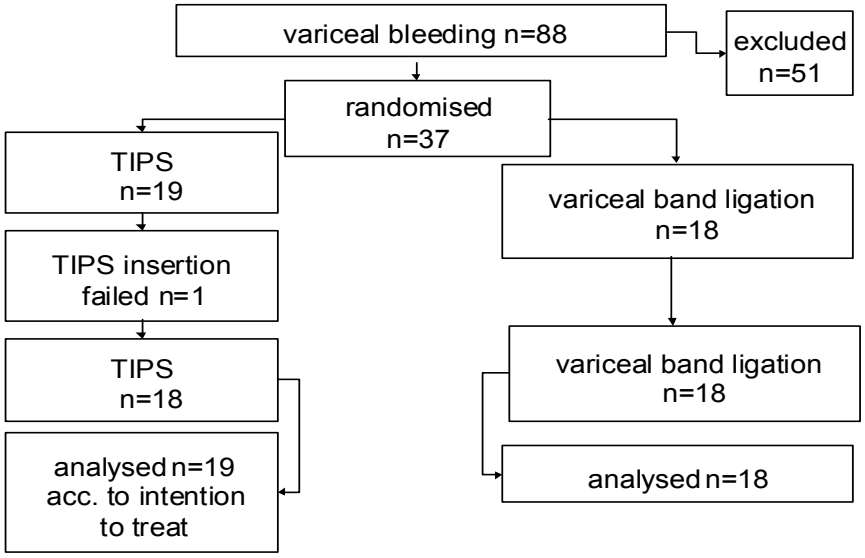

Figure 1
Trial profile

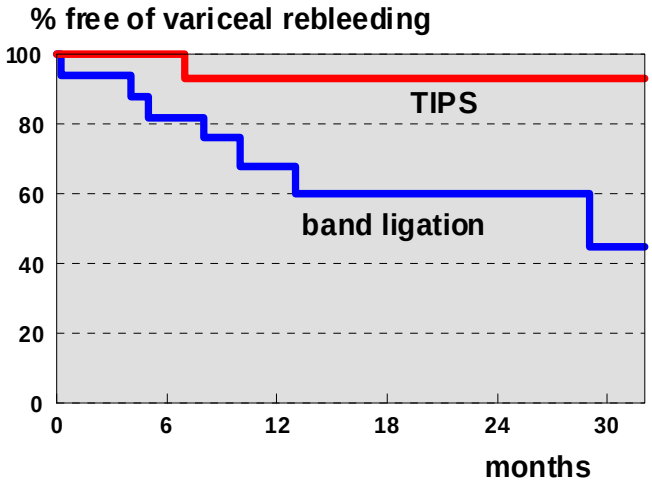

Figure 2
Kaplan-Meier plot showing the percentage of patients treated with TIPS (n=19) or variceal band ligation (n=18) remaining free of rebleeding from oesophageal varices. The difference was statistically significant (p=0.03, log-rank test).

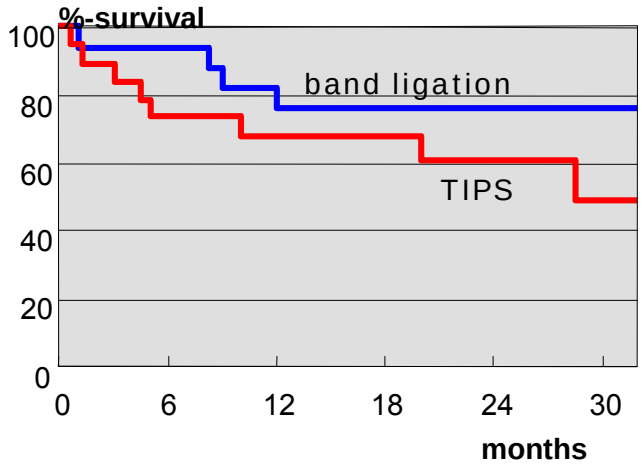

Figure 3

Kaplan-Meier plot showing the estimated survival for patients treated with TIPS (n=19) or variceal band ligation (n=18). The difference was statistically not significant.

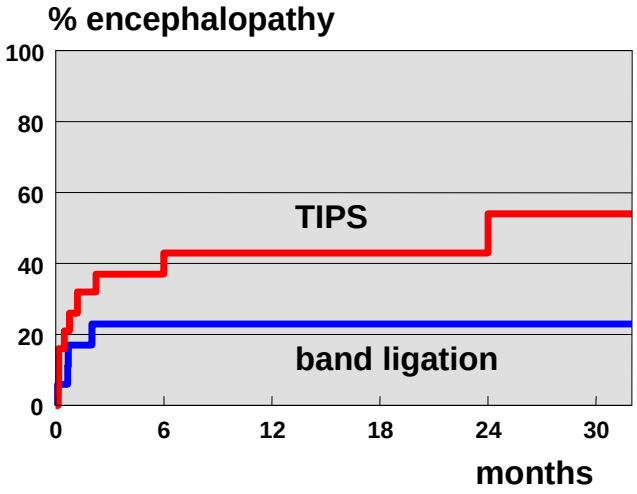

Figure 4

Kaplan-Meier plot showing the incidence of hepatic encephalopathy for patients treated with TIPS (n=19) or variceal band ligation (n=18). The difference was statistically not significant (p=0.13, log-rank test).

Table 1

Patient characteristics

Characteristic	**TIPS** n=19	**VBL** n=18
Age	50(24-75)	55(23-71)
Sex (M/F)	12/7	15/3
Diagnosis (n)		
Alcoholic liver disease	10	11
Cryptogenic cirrhosis	5	1
Hepatitis B/C	2	3
PBC/PSC	1	2
Other	1	1
Child-Pugh score	7 (5-12)	6(5-11)
Child-Pugh class A/B/C (n)	9/7/3	9/3/6
Ascites (n)	9	9
Infection (n)	0	0
Encephalopathy (n)	1	5
First variceal bleeding (n)	12	10
Gastric varices (n)	8	6
Laboratory		
Bilirubin (µmol/l)	33(11-149)	29.5(12-416)
Albumin (g/l)	32(21-45)	33.5(18-43)
Prothrombin time (sec. prolonged)	0.95(0-7.7)	0.5(0-5.4)
Platelets (x 10^9/l)	97(36-464)	88(32-374)
Creatinine (µmol/l)	67(41-106)	63(38-139)

Results are expressed as medians and ranges unless otherwise indicated

Table 2

Recurrent bleeding

	TIPS n = 19	**VBL** n = 18
Patients		
Variceal bleeding	1	7
Significant variceal bleeding	1	3
Non-variceal bleeding	3[1]	2
Episodes		
Variceal bleeding	1	9
Significant variceal bleeding	1	4

[1] 1 patient did not undergo endoscopy; despite endoscopy cause not established in 2 cases

Table 3

Causes of death

	TIPS n=19	**VBL** n=18
Liver failure	4	2
Stroke	3	
Infection[1]	1	
Pulmonary fibrosis	1	
Myocardial infarction		1
Oesophageal cancer		1
Total	9	4

[1] infected total hip arthroplasty

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7

LONG-TERM PATENCY AND CLINICAL RESULTS OF TRANSJUGULAR INTRAHEPATIC PORTOSYSTEMIC SHUNTS. OBSERVATIONS IN A PATIENT COHORT FOLLOWED FOR 3-9 YEARS

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Submitted

ABSTRACT

Background & Aims. TIPS is used to treat complications of portal hypertension. In this study the clinical results for 82 patients were evaluated.
Methods. Patients were followed for at least 3 years. 54 patients underwent TIPS for variceal bleeding, 24 for refractory ascites and 4 for other indications.
Results. TIPS placement was successful in 92%. Mean follow-up was 29.4 months. Primary patency was 22% and 12%, primary-assisted patency 67% and 46%, and secondary patency 91% and 91% at 1 and 5 years, respectively. Non-alcoholic etiology and increasing platelet counts independently predicted the development of shunt insufficiency. One and five year rate of recurrent variceal bleeding was 21% and 27%. The majority of surviving patients showed a response of ascites. The risk for encephalopathy of any degree was 25% at 1 month and 52% at 3 years. The risk for chronic or severe intermittent encephalopathy was 15% and 20% at 1 and 3 years, respectively, and age and baseline serum creatinine were independent risk factors. Overall survival was 61%, 49% and 42% at 1, 3 and 5 years, respectively. Age, serum albumin and creatinine were independently related to mortality.
Conclusions. The risk for definitive loss of shunt function was 17% at 5 years, indicating that surveillance with shunt revision when indicated results in excellent long-term TIPS patency. TIPS effectively protects against recurrent bleeding. The role of TIPS in the management of patients with refractory ascites is limited.

INTRODUCTION

During the past decade the transjugular intrahepatic portosystemic shunt (TIPS) was used increasingly for the treatment of complications of portal hypertension. The clinical effectiveness of this approach has been documented extensively (1). The duration of follow-up in most studies, however, was relatively short, with reported (mean/median) follow-up times rarely exceeding 2 years (2, 3).
Since TIPS was introduced into clinical practice in 1988 (4) it was recognized that the development of shunt dysfunction due to thrombosis or intimal hyperplasia forms the Achilles' heel of the procedure. Therefore, the role of TIPS in the long-term management of complications of portal hypertension has been questioned (5, 6). However, with regular follow-up and re-intervention when indicated, excellent 2-year patency rates of up to 90% have been reported (7-10), but the follow-up time in studies that produced Kaplan-Meier estimates of (primary, primary-assisted and secondary) shunt patency did not exceed 18 months (7-16). Therefore, long-term patency of TIPS is not well defined and it is not clear

whether the development of shunt dysfunction is a chronic, relentless problem or that its incidence decreases over time.

The aim of the present study was to assess the outcome of TIPS in a non-selected group of consecutive patients who were followed for at least three years according to a standard protocol that included repeated shunt evaluations. In particular, we assessed the pattern of (definitive) shunt loss over time and tried to identify clinical variables that predict the development of shunt insufficiency.

MATERIALS AND METHODS

Study population

From January 1992 until January 1998 TIPS placement was attempted in 82 patients. Patient characteristics are presented in table 1. The cohort of 75 patients for whom the procedure was technically successful was followed for a period of at least 3 years. Data were recorded until January 2001.

TIPS procedure

The method of TIPS insertion has been described in detail elsewhere (17) and is only summarized here. Procedures were performed under general anesthesia. All patients received intravenous antibiotic prophylaxis (1.5 grams cefuroxime) 30 minutes before the procedure. During the first year of TIPS implantation at our center, anticoagulation consisting of iv heparin was started during the procedure and continued for 1 week. This policy was abandoned after having witnessed fatal gastric variceal bleeding during heparin administration in a patient who underwent TIPS for refractory ascites.

Catheterization of the hepatic vein was performed through the right internal jugular vein. Guided by sonography and fluoroscopy, a needle was advanced through the liver parenchyma into a branch of the portal vein. A guide-wire was then passed into the portal vein and the parenchymatous tract was dilated using an angioplasty catheter. After balloon dilatation a balloon expandable (Palmaz stent, Johnson & Johnson) or self-expandable (Wallstent, Schneider, Switzerland) stent was introduced. Just before and after stent placement, pressures in the portal and caval vein were recorded and the pressure gradient was calculated. If necessary, additional balloon dilatation was performed to reduce the pressure gradient below 12 mmHg. In patients with variceal bleeding and persistent significant variceal perfusion after shunt placement, embolization was usually performed with coils.

Table 1: Patient characteristics

Total number of patients	82
Sex (M/F)	53/29
Age (median with range)	52 (24-79)
Etiology of the liver disease (%)	
Viral	15 (18)
Alcoholic	36 (44)
Viral and alcoholic	1 (1)
Cholestatic	5 (6)
Autoimmune hepatitis	3 (4)
Budd-Chiari syndrome	3 (4)
Cryptogenic	13 (16)
Other*	6 (7)
Indication for TIPS (%)	
Esophageal variceal bleeding	36 (44)
Gastric variceal bleeding	13 (16)
Ectopic variceal bleeding	5 (6)
Refractory ascites	24 (29)
Ascites and hydrothorax	2 (2)
Budd-Chiari syndrome	1 (1)
Hepatorenal syndrome	1 (1)
Child-Pugh class (%)	
A	27 (33)
B	45 (55)
C	10 (12)
Median interval bleeding-TIPS in months (range)**	0.3 (0-6.9)
Median number of prior endoscopic therapy sessions (range)**	3 (0-17)
Emergency/elective procedure**	13/41

* Other: hemochromatosis, myelofibrosis, nodular regenerative hyperplasia, alpha-1-antitrypsin deficiency

** For patients treated for variceal bleeding

Follow-up protocol

Doppler-ultrasonographic assessment of stent function was performed on days 2, 7 and 30, at 3-month intervals during the first year and every 6 months thereafter. Angiography was performed routinely at 6 months and in the event of suspected stent dysfunction, based on

clinical or ultrasonographic findings. Revision of the stent was performed when occlusion or stenosis were seen on the angiography, and also when the portocaval pressure gradient was elevated despite normal angiographic findings.

This protocol was modified in January 1997. From then on patients were subjected to routine catheterization at 1 and 6 months. This change was made in an attempt to reduce the number of patients with shunt dysfunction at 6 months.

Clinical, laboratory and other relevant data were recorded on day 7, at 1 and 3 months and subsequently at 6-month intervals.

Follow-up continued until January 2001, death or liver transplantation. Data for patients lost to follow-up or undergoing orthotopic liver transplantation were censored at the time of the last visit or at the time of transplantation.

Definitions

Primary patency was defined as patency of the stent without any reintervention. Primary-assisted patency was defined as a patent stent after reintervention, but without occlusion at any time. Secondary patency was defined as a patent stent after occlusion, which ends at the moment an untreated or untreatable occlusion is present (7). Shunt occlusion was defined as the absence of flow on ultrasonography or angiography.

Complications were defined as clinical events observed within 30 days of the TIPS procedure, which were certainly or possibly related to the procedure and required adjustment of medical management (e.g. prolongation of stay in intensive care unit or hospital, institution of antibiotic treatment). Short- and long-term complications were defined as complications occurring within 1 week of the procedure and after the first week, respectively. These complications did not include hepatic encephalopathy and shunt dysfunction, since these were recorded and analyzed separately. Variceal bleeding and rebleeding were defined according to internationally accepted criteria (18, 19). Only patients who underwent the TIPS procedure for variceal bleeding were analyzed for rebleeding.

The effect on ascites was assessed using criteria suggested by Rossle et al. (2). A complete response was defined as elimination of ascites, a partial response as persisting ascites but not requiring paracentesis and absence of response as ascites requiring paracentesis. Only patients who received a TIPS for refractory ascites were assessed for the effect on ascites.

Hepatic encephalopathy was assessed according to Opolon (20) as follows: grade I: lethargy, reversal of day-night sleep pattern, normal orientation, no flapping tremor; grade II: slurred speech, somnolence, inadequate behavior, difficult handwriting, flapping tremor; grade III: disorientation in time, place or person, pre-coma; grade IV: coma. Chronic encephalopathy was defined as clinical encephalopathy which did not respond to medical

treatment and a protein-restricted diet. Severe intermittent encephalopathy was defined as disabling intermittent encephalopathy despite treatment.

Statistical analysis

Data processing and analysis were performed using SPSS version 9. Student's t-test was used to analyze differences between groups. Encephalopathy, shunt patency, survival and rebleeding curves were created according to Kaplan and Meier and compared by means of the log-rank test. Cox regression analysis was performed to assess factors related to encephalopathy, shunt patency and mortality. Logarithmic transformations (base 10) of serum creatinine levels and platelet counts were used. The Cox proportional hazards model was applied to assess factors independently related to encephalopathy, patency and mortality. We included those factors found to be significant or showing a trend ($p< 0.1$) in the univariate analysis. Non-significant factors in the multivariate analysis were subsequently removed until factors with independent prognostic significance remained. A two-tailed p-value ≤ 0.05 was considered significant.

RESULTS

Creation of a functional stent was achieved in 75 of the 82 patients (91%).

Three of the seven unsuccessful procedures occurred within the first year of introduction of the technique. Reasons for failure were: unsuccessful puncture of the portal venous system (n=5), intraperitoneal bleeding due to perforation of the extra hepatic portal vein (n=1) and stent occlusion during placement (n=1). The mean duration of follow-up was 29.4 ± 29.5 (range 0.3 – 105.5) months. Patients (n=22) who were still in the study at the end of the follow-up period had been followed for a mean of 60.1 ± 21.5 months. Two patients were lost to follow up at 1 and 32 months. Six patients underwent liver transplantation after 1, 2, 3, 12, 27 and 74 months, respectively.

Complications

Short-term complications occurred in 16 patients (Table 2). They proved to be fatal in three cases: one patient died from heart failure, one from sepsis and one from intraperitoneal bleeding. A long-term complication, sepsis occurring 15 days after TIPS placement, was observed in one case. Another potential complication was pulmonary hypertension, observed in one case after 14 months (21).

Table 2: Short-term complications

Complication (no. of patients)
Sepsis (3)
Intraperitoneal bleeding (3)
Aspiration pneumonia (2)
Jugular vein hematoma (2)
Thrombocytopenia (1)
Hemolysis (1)
Hemobilia (1)
Liver capsule perforation (1)
Hematothorax (1)
Heart failure (1)
Bleeding of arterial line (1)

Shunt patency

The portocaval pressure gradient decreased from a mean of 15 mmHg before the TIPS procedure to a mean of 7.3 mmHg after successful placement of the TIPS ($p<0.0001$).

The median number of TIPS recatheterizations was 1 (range 0-6); the median number per patient follow-up year was 0.5. Patency curves are shown in figure 1. The primary patency rate was 22% at 1 year, 17% at 2 years and 12% at 4 and 5 years. The primary-assisted patency rate was 67% at 1 year, 62% at 2 years, 51% at 4 years and 46% at 5 years. The secondary patency rate was 91% at 1 year, 86% at 2 years, and 83% at 4 and 5 years.

The following factors were included in univariate Cox regression analyses of primary, primary-assisted and secondary TIPS patency: age, sex, serum bilirubin, serum creatinine, platelet count, Child-score, diabetes mellitus, ascites, alcoholic versus non-alcoholic etiology, Wall-stent versus Palmaz stent and portal pressure gradient, portal pressure and caval vein pressure before and after TIPS insertion. Platelet count and alcoholic etiology were found to be significant predictors of the primary patency in both univariate and multivariate analyses (Table 3). Thus, alcoholic etiology and lower platelet count were predictive for the absence of shunt failure. No significant predictive factors were found for the primary-assisted or secondary patency rate.

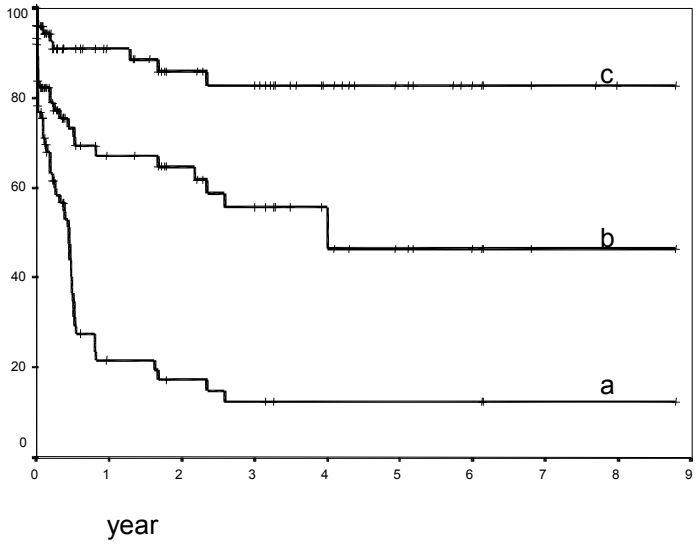

Figure 1: Kaplan-Meier plot showing the primary (a), primary-assisted (b) and secondary (c) patency rate in years for the TIPS among 75 patients.

Table 3: Multivariate analysis

	Hazard ratio	95% Confidence interval	P-value
Survival			
Age (years)	1.03	1.00-1.05	0.03
Serum albumin (g/l)	0.95	0.91-0.99	0.02
Log_{10} serum creatinine (μmol/l)	11.95#	3.60-39.71	0.0001
Hepatic encephalopathy			
Encephalopathy before TIPS	8.88	3.01-26.21	0.0001
Age (years)	1.04	1.01-1.07	0.01
Alcoholic etiology	0.36	0.16-0.80	0.007
Severe intermittent or chronic encephalopathy			
Age (years)	1.07	1.01-1.14	0.018
Log_{10} serum creatinine (μmol/l)	34.43#	4.08-290.43	0.001
Primary shunt patency			
Log_{10} platelet count (10^9/l)	4.12#	1.52-11.18	0.006
Alcoholic etiology	0.43	0.23-0.79	0.007

effect of 10-fold increase

Hepatic encephalopathy

Fifteen patients (20%) had experienced encephalopathy sometime before receiving TIPS. At the time of TIPS placement, 7 (9%) patients had clinical evidence of encephalopathy. In three of these cases encephalopathy became a chronic problem while it was transient in the others.

After introduction of the TIPS, 37 (49%) patients developed a new episode of clinical encephalopathy. Grade I encephalopathy occurred in 32%, grade II in 30%, grade III in 14% and grade IV in 14% of the patients. In 4 cases the grade of encephalopathy was not recorded. Most cases could be managed successfully by correction of the precipitating factors and administration of lactulose. Antibiotic treatment and/or a protein-restricted diet were instituted when symptoms persisted. Chronic or severe intermittent encephalopathy occurred in 12 patients; the median age of this group was 64 years. Nine of these 12 patients died due to hepatic failure, 2 due to infections; 1 underwent liver transplantation.

The risk for encephalopathy of any degree was 25% at 1 month, 40% at 6 months, 44% at 1 year, 47% at 2 years and 52% at 3 years (Figure 2, A). The risk for chronic or severe intermittent encephalopathy was 15%, 18% and 20% at 1, 2 and 3 years, respectively (Figure 2, B). There was no significant difference in shunt diameter between patients who did and did not develop encephalopathy after receiving a TIPS (8 vs. 9.5 mm, p=0.25).

The following factors were included in univariate Cox analyses of encephalopathy: age, sex, alcoholic versus non-alcoholic etiology, serum bilirubin, serum creatinine, Child-Pugh score, ascites, encephalopathy prior to and at the time of TIPS placement, portal pressure gradient before and after TIPS insertion and stent diameter. Age, non-alcoholic etiology, encephalopathy prior to and encephalopathy at the time of TIPS placement, Child-Pugh score and creatinine were all found to be predictors of encephalopathy. Multivariate analysis showed that age, non-alcoholic etiology and encephalopathy at the time of TIPS placement were the main factors independently related to development of post-TIPS encephalopathy (Table 3). Alcoholic etiology, lower age and absence of HE before the TIPS procedure were favorable factors regarding the development of encephalopathy after TIPS.

Univariate analysis for chronic or severe intermittent encephalopathy showed that age, creatinine and encephalopathy prior to TIPS were predictive factors. In multivariate analysis, however, only age and serum creatinine remained as independent predictors for the development of chronic or severe intermittent encephalopathy.

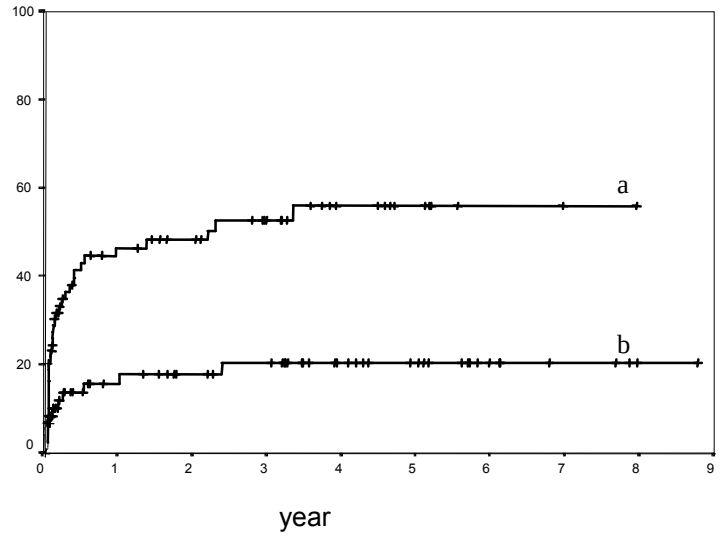

Figure 2: Probability of developing hepatic encephalopathy of any degree (a) and chronic or severe intermittent hepatic encephalopathy (b) in years for 75 patients who underwent a TIPS procedure (inverse Kaplan-Meier plot)

Rebleeding

Recurrent bleeding from varices and due to non-variceal causes was observed in 10 (21%) and 9 (19%) of the 48 patients, respectively, who successfully underwent the TIPS procedure for secondary prevention of variceal bleeding. In one case variceal rebleeding occurred after 48 months; venography showed total occlusion and a new, parallel TIPS was inserted. Nine out of ten cases of variceal rebleeding occurred within 6 months (mean 51 days, range 1 - 173) of TIPS insertion. In two of these cases total shunt obstruction was due to thrombosis and intimal hyperplasia, respectively, and TIPS revision was performed. In another two cases shunt stenosis, but without total obstruction, was treated with balloon angioplasty. In one case of rebleeding 1 day after TIPS insertion, Doppler ultrasonography showed normal TIPS function. TIPS catheterization was not performed and the patient underwent endoscopic injection therapy. In the remaining four cases of variceal rebleeding, portal venography showed no abnormalities and portal-caval vein pressure gradients were below 12 mmHg. However, venography showed the presence of patent collaterals, in particular significant persistent portal blood flow via the coronary vein in three cases and via the inferior mesenteric vein in one case. The latter patient had received a TIPS for recurrent bleeding from anorectal varices. Embolization of the collaterals was performed in all four cases.

A second episode of recurrent gastro-esophageal variceal bleeding occurred in two cases. In one patient balloon dilatation for shunt stenosis had been performed 6 days earlier after a first recurrence of hemorrhage; this patient was in a very poor condition and died shortly afterwards. In the other patient TIPS function was normal but portal venography showed persistent significant collateral blood flow. For technical reasons embolization was unsuccessful. During the subsequent 5-year follow-up this patient suffered no recurrences.
The 1-, 2- and 5-year rates of recurrent bleeding from varices were 21%, 21% and 27%, respectively (Figure 3).

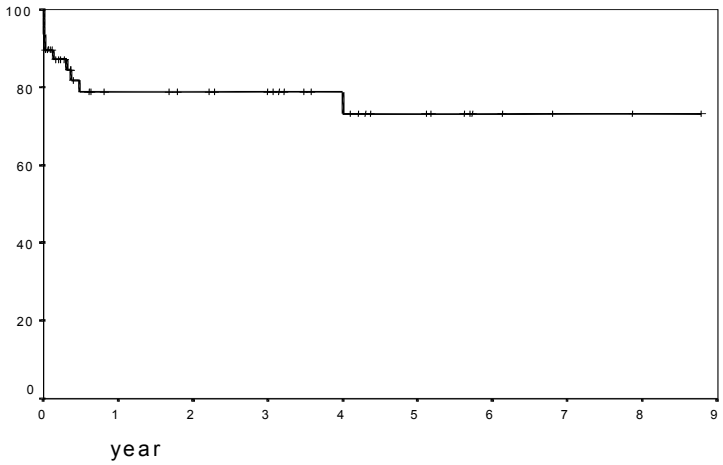

Figure 3: Kaplan-Meier plot showing the probability of remaining free of rebleeding in years for 48 patients who underwent a TIPS procedure for variceal bleeding

Ascites

The TIPS was successfully introduced in all but one case of refractory ascites. Table 4 summarizes the response to the TIPS at 1, 3, 6, 12 and 36 months. For these 23 patients mortality at 6 months was 43%; at 3 years 14/23 patients (61%) had died. Causes of death were liver failure (n=7), renal failure (n=2) that was already apparent before the TIPS procedure, variceal bleeding (n=2), pneumonia (n=2), and hepatocellular carcinoma (n=1). Two patients underwent liver transplantation. Among survivors a complete or partial response was observed in the majority of cases. For these patients diuretic therapy was reduced significantly.

Table 4: Data on clinical course and response to TIPS for 23 patients with refractory ascites

	Month				
	1	3	6	12	36
complete response	6	6	3	3	4
partial response	6	4	6	4	1
non-response	7	4	2	2	1
Dead	3	7	10	11	14
Transplantation	0	1	1	2	2
lost to follow-up	1	1	1	1	1

Survival

Two patients died within the first week, one from hepatorenal syndrome and sepsis and one, treated for refractory ascites, from massive gastric variceal bleeding while receiving intravenous heparin. During follow-up 45/75 (60%) patients died. Causes of death were liver failure (n=19; 42%), variceal bleeding (n=4; 9 %) and other causes (n=22; 49%). Survival at 1 month was 88%, at 6 months 68%, at 1 year 61%, at 3 years 49% and at 5 years 42% (Figure 4).

The following factors were included in univariate Cox regression analyses: sex, age, presence of ascites, history of encephalopathy, indication (variceal bleeding vs. other), serum creatinine, albumin and bilirubin, platelet count and Child-Pugh score. Age, ascites, creatinine, albumin and Child-Pugh score were all found to be significant predictors of survival. Multivariate analysis of these factors with backward elimination showed that age, serum albumin and serum creatinine were the most important factors independently related to mortality (Table 3).

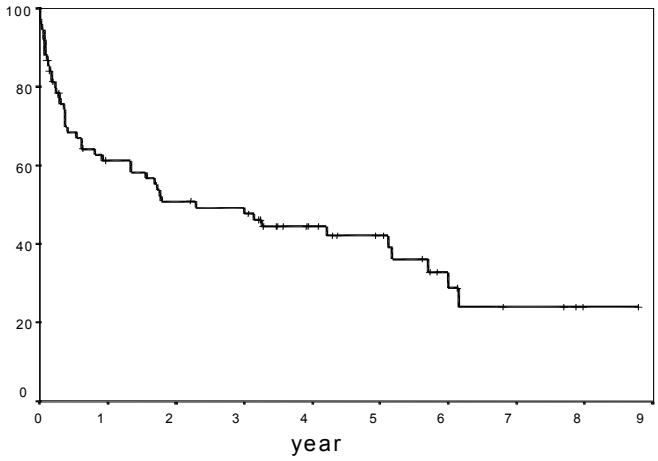

Figure 4: Kaplan-Meier plot of survival following TIPS insertion in 75 patients (years).

DISCUSSION

The present study confirms that introduction of the TIPS is not a single-step procedure and that repeated interventions are required to maintain function in a large majority of the patients. However, our data also show that efforts to maintain TIPS function can eventually result in good long-term patency and suggest that (definitive) shunt loss 3-4 years after the TIPS procedure is rare. We observed a shunt loss of 17% at 5 years. This may not be markedly different from the reported figures for surgical shunts, which ranged from 11-20% (22-27). Our data are compatible with earlier suggestions that in a subset of patients pseudo-intimal proliferation may be a self-limiting process (10) and that the necessity for shunt revisions may decrease over time (28).

Up until now no generally accepted guidelines for shunt surveillance have emerged, and follow-up protocols differ from center to center (7, 15, 17). Most centers use both ultrasonography and venography, but the optimal sequence and time intervals remain to be established. In general, ultrasonography is non-invasive, inexpensive and simple but compared to angiography, an invasive and expensive procedure, the sensitivity and specificity for detecting shunt dysfunction may be less (29). Local experience and expertise are likely to be of decisive importance in the choice of the optimum protocol for a given center. Recent developments in ultrasonography, such as contrast-enhanced Doppler sonography and power Doppler sonography, might increase the value of this technique for detecting shunt dysfunction (30, 31).

When interpreting data on primary and secondary shunt patency, the influence of the type of surveillance method should be taken into account. It is conceivable that centers using routine angiography are likely to do more (early) reinterventions, resulting in lower primary patency rates. Therefore, for the interpretation of the results of individual studies, reported secondary patency rates may be more informative.

Previous studies reported a number of risk factors for developing shunt insufficiency, including diabetes mellitus (32), biliary-venous fistulae (9, 33), female sex (32), age over 55-65 years (32), Child-Pugh score (34), low prothrombin times (17), high platelet counts (17), a porto-caval pressure gradient > 18 mmHg prior to the TIPS procedure (35) and portal vein pressure (36). We identified non-alcoholic liver disease and platelet count as risk factors for developing shunt dysfunction. A role of platelets was not supported by the findings of a controlled trial evaluating acetylsalicylic acid for the prevention of shunt occlusion (37). In contrast, a significant reduction in the incidence of shunt stenosis was reportedly achieved by combined treatment with ticlopidine, a platelet aggregator inhibitor, and trapidil, a drug with anti-platelet-derived growth factor activity (38). (Moderate) consumption of alcohol, particularly red wine, has been reported to decrease the risk for peripheral (39),

cardiovascular and cerebrovascular arterial disease (40, 41). Alcohol may also decrease the risk for venous thromboembolic events (42). One mechanism by which alcohol could have an effect on vascular disease is through inhibition of platelet reactivity (43). Clearly, findings on risk factors for developing TIPS insufficiency have been far from consistent. Both this study and other studies suggest that the absolute number of platelets (17) as well as platelet function (38) may be implicated. Further studies are needed to address the potential role of platelets and the medical modulation of platelet involvement. In addition, technical innovations such as the introduction of less thrombogenic, covered or drug-eluting stents are important in attempting to find a solution for the critical problem of shunt obstruction (44-46).

Hepatic encephalopathy is an inherent problem of portosystemic shunting. Reported risk factors are age (17, 47-49), bleeding (50) and encephalopathy prior to the TIPS procedure (34, 35, 48), Child-Pugh score (34), non-alcoholic etiology (50, 51), female sex (51), hypoalbuminemia (51) and a portocaval pressure gradient < 10 mmHg after TIPS placement (49). In the present study, risk factors for the occurrence of encephalopathy after the TIPS procedure were encephalopathy prior to the introduction of the TIPS, increasing age and non-alcoholic etiology of the underlying liver disease. Age and encephalopathy prior to TIPS are well recognized factors, but the lower risk for encephalopathy in alcoholic cirrhosis, that was also found by others (51), is difficult to explain, considering that shunt patency in alcoholic patients was better and the incidence of subclinical encephalopathy in these patients may be higher (52). In approximately one-third of the patients with encephalopathy after a TIPS procedure, it was chronic or present intermittently. Independent risk factors were increasing creatinine and age over 65 years. In patients over 65 years and those with elevated creatinine levels the indication for TIPS should be considered very carefully and extra care should be taken to prevent, detect and treat encephalopathy.

Our results for patients receiving a TIPS for refractory ascites are in agreement with previously reported data (53-58) and show that in a number of cases the TIPS may provide long-term control of previously refractory ascites. However, the general prognosis for patients with refractory ascites is grave, with reported one-year survival rates after the TIPS procedure not exceeding 30-50 percent (53-55, 57). This underlines the fact that liver transplantation should always be the primary therapeutic approach for this patient group. Two of our patients received a TIPS while having long-standing organic (non-hepatorenal) kidney disease with renal insufficiency. The TIPS was ineffective and both patients died within 4 months. This experience is comparable to that reported by others (54, 55, 58) and confirms that for patients with chronic renal insufficiency, e.g. with a serum creatinine level of more than 200 µmol/l, a TIPS is not suitable as treatment for refractory ascites. Two studies (2, 57) have compared the TIPS with large-volume paracentesis, a procedure that is often regarded as the treatment of choice for refractory ascites. The TIPS was found to have a

beneficial effect on ascites; this was associated with an improvement in transplantation-free survival but not with an increased risk for encephalopathy in the largest trial (2). Currently available data indicate that the TIPS is a reasonable therapeutic option for patients with refractory ascites. Patients over 60-65 years of age and those with chronic renal impairment are unlikely to benefit from a TIPS; repeated paracentesis seems to be a better alternative in such cases.

In conclusion, after a TIPS procedure, regular surveillance with shunt revision when indicated can eventually result in excellent long-term patency. In our study the risk for definitive shunt loss was 17% at 5 years. The TIPS effectively protects against rebleeding in the majority of patients with variceal bleeding. Recurrent variceal hemorrhage is usually due to shunt insufficiency but persistent significant perfusion of portosystemic collaterals is another important cause. Severe encephalopathy can be expected to occur, particularly in patients over 65 years of age and in those with renal impairment.

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8

A COHORT STUDY OF ECTOPIC VARICEAL BLEEDING INDICATING UNSATISFACTORY RESULTS OF LOCAL THERAPIES

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Submitted

SUMMARY

Objectives: to assess the results of a therapeutic strategy for initial local therapy followed by a shunting procedure, if indicated, for patients with portal hypertension and bleeding ectopic varices. To report our experience over an eighteen-year period with this uncommon condition.

Design: cohort study

Setting: University hospital; referral centre for liver diseases

Participants: 22 consecutive patients with bleeding from colorectal, duodenal, jejuno-ileal, stomal, intraperitoneal and cutaneous varices

Main outcome measures: recurrence of bleeding

Results: Diagnosis and appropriate treatment were frequently delayed, particularly in cases of intraperitoneal, jejuno-ileal and rectal variceal bleeding. The probability of renewed bleeding after local therapeutic procedures (n=19) was 61% at 1 month and 80% at 6 months. After introduction of second-line therapy (shunting procedures) recurrence occurred in 18% at 6 months and 27% after 1 and 5 years. Two patient treated primarily with a surgical shunt did not suffer a recurrence.

Conclusion: For patients with portal hypertension and bleeding not explained by gastro-oesophageal varices, the possibility of ectopic variceal bleeding should always be considered. Local therapies frequently fail. Shunt procedures seem to be the best therapeutic approach and may be required in the majority of patients. However, shunt procedures may not always be possible and other therapies may occasionally also provide long-term control of bleeding.

INTRODUCTION

Ectopic varices can be defined as varices occurring anywhere except in the cardio-oesophageal region, the preferred site for the development of portosystemic collateral veins in patients with portal hypertension. Bleeding from these varices, which has been observed throughout the gastrointestinal tract but also in the genitourinary and biliary tracts, the abdominal wall, the peritoneal cavity, the skin and the lung (1-3), has been estimated to account for between 1% and 3% of all variceal haemorrhages (1). Literature on this subject consists mainly of case reports and small series, the largest consisting of 17 cases of bleeding from stomal varices (4). The rarity of the condition and the absence of controlled trials of therapeutic modalities explain why the long-term course and optimal management are poorly defined. This report describes experience in a single institution with ectopic

variceal bleeding over an eighteen-year period, focussing on the therapeutic results of a two-step therapeutic strategy.

PATIENTS AND METHODS

This series includes all consecutive patients diagnosed with bleeding from ectopic varices between January 1984 and December 2001. During this period our therapeutic strategy consisted of an initial local, non-shunting procedure, aimed at obtaining haemostasis and prevention of renewed bleeding, followed by a surgical or transjugular intrahepatic portosystemic shunt (TIPS), if the initial approach failed. TIPS was the preferred shunting method after this procedure was introduced in our hospital in 1991. For patients with intraperitoneal variceal bleeding, local procedures were considered inappropriate (1) and therefore a shunt procedure was the therapy of first-choice. Local therapies included (endoscopic) injections of either 2% etoxysclerol or bovine thrombin or combinations of these agents, endoscopic band ligation, surgical ligations, reinsertion of enterostoma, subtotal colectomy and segmental small-bowel resection.

At the time of diagnosis patient data were recorded; subsequently the database was updated on a yearly basis with respect to clinical course and therapies. Follow-up ended on 1 December 2001. Patients lost to follow-up were censored at the time of the last consultation. For patients receiving a liver transplant follow-up ended at the date of surgery. Recurrent bleeding and mortality were analysed using the Kaplan-Meier method.

RESULTS

During the study period 22 patients were diagnosed with ectopic variceal bleeding (table 1). The total number of new cases of variceal bleeding was about 540, resulting in an estimated 4% prevalence of bleeding from ectopic sites. The mean duration of follow-up was 48 ± SD 58 months (range 3 days – 18 years). Two patients were lost to follow-up after 12 months.

Diagnostic aspects

In seven of eight patients with colorectal varices, bleeding was a recurrent problem that had required repeated hospital admissions and blood transfusions. In all, blood loss was initially attributed to haemorrhoids and haemorrhoid surgery had been performed previously in six cases without success. In four cases, varices were associated with anal prolapse. The diagnosis was based on endoscopic and visual inspection (5); additional endorectal ultrasound, technetium erythrocyte scanning and angiography was performed each in one case. In our experience, stomal varices were usually not clearly visible on (endoscopic) inspection. Submucosal collaterals were visualised by means of ultrasound examination

while active and, occasionally spurting, bleeding from tiny red mucosal spots was observed on at least one occasion in each case. The diagnosis for patients with duodenal varices was made endoscopically while cutaneous variceal bleeding was diagnosed by observing actual bleeding from, ultrasound-verified, cutaneous collaterals. Intraperitoneal variceal bleeding was diagnosed when free intrabdominal blood was found in the presence of peritoneal collaterals in the absence of other potential causes during laparotomy. In one case of a man who suddenly succumbed at home this was a post-mortem diagnosis. In another case this diagnosis was only considered seven weeks after a first intraperitoneal haemorrhage and one week after a second episode and a 'negative' exploratory laparotomy. In our three cases of ileal and jejunal variceal bleeding the possibility of the diagnosis was not even considered for several weeks. Diagnosis was based on the exclusion of other potential causes of bleeding and confirmed by radioactive red cell scanning showing blood accumulation within the small bowel and findings during laparotomy, including peroperative enteroscopy.
Nine of our 22 patients - four with stomal, three with jejuno-ileal and two with cutaneous varices - had undergone previous abdominal surgery, that had induced and could explain the development of varices either at the site of an enterostomy or adhesions (1).

Initial treatment

Two patients diagnosed with intraperitoneal variceal bleeding received a surgical portocaval shunt after 7 days and 10 weeks, respectively, while bleeding in another case was fatal. In all other nineteen patients a local therapy was instituted. Six of the eight patients with rectal variceal bleeding were treated initially with injection sclerotherapy (etoxysclerol 2%, in two combined with bovine thrombin) or band ligation (n=1); in one patient varices were treated with surgical sutures and another patient underwent emergency subtotal colectomy for massive bleeding from varices associated with portal venous thrombosis. Three of the four patients with stomal varices were treated with injection sclerotherapy and in one case the stoma was reinserted. The two patients with duodenal variceal bleeding and one patient with cutaneous variceal bleeding received injection sclerotherapy; in one patient with cutaneous variceal bleeding local treatment consisted of surgical sutures. In the three cases of jejuno-ileal variceal bleeding segmental small-bowel resection was performed. In the latter condition the a priori preferred therapy was a shunt procedure; however, this proved impossible due to either extensive thrombosis of the portal venous system (n=2) and/or a poor clinical condition (n=2).

Recurrent bleeding

After local treatment, bleeding did not recur in 5/19 patients: one case each of duodenal (injection sclerotherapy), rectal (band ligation) and cutaneous varices (injection

sclerotherapy) and two cases of ileal varices (segmental small-bowel resection) during a mean follow-up of 41.5 months (range 0.2 - 123). In 14 /19 (74%) cases of colorectal, small-bowel, stomal and cutaneous varices recurrent bleeding after local treatment was observed. The probability of renewed haemorrhaging after 1, 2 and 6 months was 61%, 75% and 80%, respectively (figure 1). Second line therapy - TIPS in seven cases, a surgical shunt in three and restoration of the continuity of the bowel in a patient with enterostomal varices - was instituted after 0.5 - 18.5 (mean 4.2) months, after 1-4 (mean 3) recurrent haemorrhages and administration of 0 - 31 (mean 7.5) units of packed red blood cells; at that time local treatment had been repeated in ten cases (eight underwent 2 local procedures, two 3 procedures). Two patients with rectal varices had not received blood transfusions before a TIPS procedure was carried out. They had suffered multiple bleedings resulting in chronic anaemia and had invalidating mechanical complaints associated with large anorectal varices. Despite recurrent bleeding second-line therapy was not introduced in three cases because blood loss was minor (n=1) or shunting procedures were not possible (n=2). After introduction of second-line therapy mild anorectal bleeding and discomfort in the presence of anal prolapse persisted, following TIPS, in three patients. In one of these cases additional embolization of the inferior mesenteric vein was performed. The probability that renewed bleeding will not occur after second-line therapy was 82% after 0.5 years and 73% after 1 and 5 years (figure 1).

Two patients diagnosed with intraperitoneal variceal bleeding remained free of recurrent bleeding after portocaval shunt surgery during 3.3 and 7 years of follow-up.

Mortality

The 1, 2 and 5 year survival rates were 73%, 57% and 41%, respectively. Thirteen patients died, one from massive intraperitoneal variceal bleeding. Other causes of death included liver failure (n=5), gastric variceal bleeding, hepatocellular carcinoma, colon cancer, lung cancer, stroke and myelofibrosis. In one case the cause remained unknown.

Patients with non-cirrhotic portal hypertension

Non-cirrhotic portal hypertension was diagnosed in 6 patients. Three patients with portal vein thrombosis were observed with bleeding from duodenal, rectal and ileal varices in one case each. No recurrence of bleeding occurred in those patients with duodenal and ileal varices after local therapies, injection sclerotherapy and ileal segment resection, respectively. The patient with rectal varices underwent subtotal colectomy after massive bleeding. Due to extensive thrombosis of the portal venous system decompressive surgery was not possible. He continues to have chronic blood loss from ileo-rectal varices and requires intravenous iron therapy.

Three patients had non-cirrhotic portal hypertension due to myelofibrosis, nodular regenerative hyperplasia and idiopathic portal hypertension. The patient with the latter condition was confirmed to bleed from ileal varices during laparotomy and underwent local segmental resection. This patient with a history of diabetes mellitus, wide-spread atherosclerotic vascular disease, myocardial infarction, bronchial carcinoma and gastric lymphoma was in a particular poor condition and a shunt procedure was not considered feasible; he died 6 weeks after surgery without having had recurrent bleeding. The other two patients had rectal variceal bleeding that recurred on several occasions after injection sclerotherapy. After TIPS, mild intermittent blood loss persisted; in one case additional embolization of the inferior mesenteric vein was performed.

DISCUSSION

Our study indicates that local therapies frequently fail to provide long-term control of bleeding from ectopic varices and suggests that procedures aimed at lowering portal pressure are more effective and may be necessary in the majority of patients. However, as a result of local anatomy, in particular extensive thrombosis of the splanchnic venous system, concomitant diseases and the condition of the patient, this may not always be feasible.

This was a long-term follow-up study of all consecutive patients presenting with bleeding ectopic varices in our hospital. This may have prevented potential biases associated with previous case series, in particular selective reporting of successfully managed patients or preliminary conclusions with respect to therapeutic results. Although we found that the efficacy of shunting procedures seems to be superior to local, non-shunt procedures, these observations should nevertheless be interpreted with caution since this was not a randomised controlled investigation to compare these treatment options.

Our experience with colorectal and stomal variceal bleeding is in agreement with other reports (6-9) but more favourable results of local therapies have also been described (10-12). Local therapies may not always be safe since two of our patients with previous mild bleeding suffered a life-threatening haemorrhage following local injection therapy and required TIPS as an emergency procedure. Another case experienced massive bleeding after local suturing of rectal varices and underwent emergency shunt surgery. Even after shunting, varices may persist due to major portosystemic shunting via the inferior mesenteric vein, and obliteration of this afferent vein may be required (13). For stomal varices, removal of the stoma and restoration of the continuity of the bowel may be a simple solution; however frequently this is not a feasible option.

In our experience the possibility of small-bowel, intraperitoneal and rectal variceal bleeding, in particular, is often not considered as a potential cause of gastrointestinal bleeding in

patients with portal hypertension, resulting in delays in diagnosis and proper management. Intraperitoneal variceal bleeding is associated with high mortality (1) and, once diagnosed, should result in the construction of a portosystemic shunt as soon as possible. Probably, small bowel variceal bleeding should be treated in the same way. As illustrated by two of our cases, relatively simple surgery with local resection of the involved segment and disconnection of intestinal-peritoneal adhesions and collaterals may also provide sustained control of bleeding when shunting procedures are not possible.

This study confirms that rectal varices continue to be misclassified as haemorrhoids (5,10). Rectal blood loss in a patient with portal hypertension and 'haemorrhoids' should be considered to be of variceal origin until proven otherwise. Transrectal ultrasonography now seems to be the diagnostic method of choice in case of doubt regarding the nature of anorectal vascular abnormalities (14).

Embolisation of feeding portal collaterals has been proposed as a potential important therapeutic modality for bleeding ectopic varices (12,15). Our experience with this approach is limited since embolisation was performed in only one case (13). Given the necessity of gaining access to the portal venous system, either by a transjugular or transhepatic approach, we feel that in most cases it may be wiser to choose a TIPS procedure since it basically addresses the underlying problem of portal hypertension (9).

Propranolol was reported to be ineffective in six patients with stomal varices (16). We are not aware of other data regarding the use of pharmacological therapy for ectopic variceal. In the current series propranolol or other vasoactive drugs were not used. Obviously, there is ample room for further evaluation of the effects of pharmacological, as well as other, therapies. Considering the rarity of ectopic variceal bleeding, multicentre collaboration seems a prerequisite for conducting meaningful studies.

In summary, when confronted with patients with portal hypertension and haemorrhage, which cannot be explained by gastro-oesophageal varices, the possibility of ectopic variceal bleeding should always be a main consideration. In our experience local therapeutic procedures frequently fail to provide long-term control of bleeding. Therefore, a portosystemic shunt procedure should probably be considered in all cases. If this is not possible a number of other therapies may occasionally be successful.

Table 1 Patient characteristics

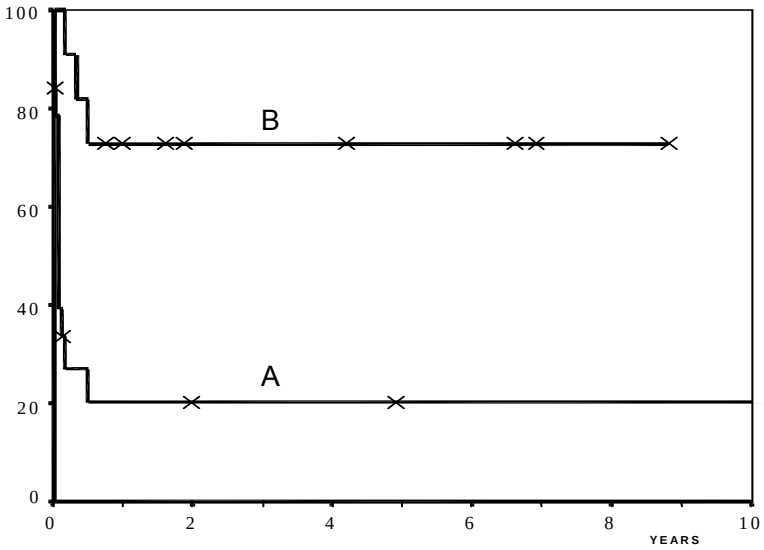
	n=22
age (years; mean, SD, range)	52.1 ± 15 (24-79)
females/males	7/15
aetiology of portal hypertension	
portal vein thrombosis	3
cirrhosis:	
- alcohol	7
- PBC	3
- PSC	3
- autoimmune hepatitis	1
- hepatitis B	1
- hepatitis C + portal vein thrombosis	1
nodular regenerative hyperplasia	1
myelofibrosis	1
idiopathic portal hypertension	1
Child-Pugh class[1] A/B/C	9/7/3
previous gastro-oesophageal variceal bleeding	7
location of ectopic varices	
- rectum	8
- stoma	4
- intraperitoneal	3
- duodenum	2
- jejunum	1
- ileum	2
- skin	2
transfusions[2] (mean; SD, range)	10.8 ± 25 (0 - 118)

[1]not determined for patients with portal vein thrombosis

[2] units of packed red cells administered during initial bleeding episode in our hospital

Figure 1

Kaplan-Meier plot representing the proportion of patients without recurrent bleeding after local therapies (A; n=19) and second line therapy (B; n=11).



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9

BILE DUCT LESIONS IN PORTAL VEIN THROMBOSIS

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ABSTRACT

Four patients with portal vein thrombosis, three men of 51, 45 and 31 years and one woman of 22 years, presented with symptoms or signs of biliary obstruction. Laboratory investigations revealed cholestasis. Cholangiography demonstrated smooth indentations of the common bile duct consistent with external compression by collateral veins. The clinical course varied from spontaneous resolution of both symptoms and serum biochemical abnormalities to persistent cholestasis. In two cases, surgical treatment (splenorenal shunt and hepaticojejunostomy) failed due to the presence of numerous collateral veins. Biliary strictures secondary to the formation of a portal cavernoma, so-called portal biliopathy, is a fairly unknown complication of portal vein thrombosis. Although the majority of patients are asymptomatic, porto-systemic shunt surgery or endoscopic biliary intervention may be indicated in symptomatic cases.

Introduction

A network of collateral veins may develop in the hepatoduodenal ligament following thrombosis of the portal vein (1-3). Ultrasonographic imaging of this conglomerate of veins, which is called a portal cavernoma or cavernomatous transformation of the portal vein, may produce a characteristic picture (Fig 1).

The most frequent complication of portal vein thrombosis is bleeding from oesophageal or gastric varices (1, 4) or, less common, from ectopic varices in the duodenum or rectum (5). A rare and relatively unknown complication of portal vein thrombosis, involving the biliary tract, will be discussed by means of the case histories described below.

Case histories

Patient A, a 51-year-old male, presented with oesophageal variceal bleeding 20 years ago. Treatment consisted of a splenectomy. Portosystemic shunt surgery failed due to massive per-operative blood loss from collateral veins. On the basis of histological, ultrasonographical and angiographical examinations the diagnosis ‘thrombosis of the portal and superior mesenteric veins’ was made. A cause could not be identified.

Ten years ago, he presented for the first time with abdominal pain, jaundice, dark urine and discoloured stools. Laboratory investigations revealed cholestasis (Table I). Endoscopic retrograde cholangiopancreatography (ERCP) demonstrated multiple strictures of the common bile duct. A diagnosis of primary sclerosing cholangitis was considered likely.

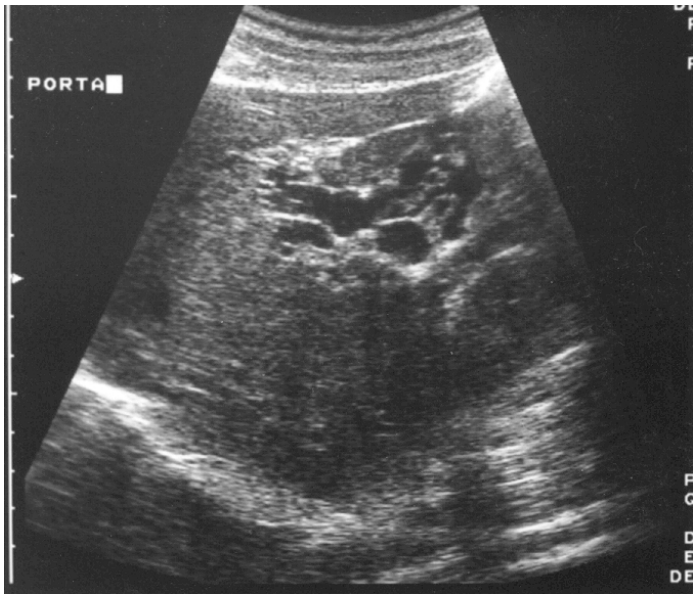

Figure 1. Ultrasonography of a portal cavernoma.

Within two weeks symptoms disappeared and serum liver tests normalized. Two years later, the same signs and symptoms recurred. At ERCP small intrahepatic stones were found in addition to the previously known abnormalities. A nasobiliary drain (Fig 2) was introduced for lavage of the biliary tree. Treatment had to be stopped because of the development of fever 24 hours later. The symptoms disappeared after antibiotic therapy and the patient was discharged in good general condition. After a duodenal variceal haemorrhage 1 year later and recurrent oesophageal variceal bleeding 2 years later, endoscopic sclerotherapy was initiated resulting in variceal eradication. One year ago he presented again with jaundice. ERCP revealed small concrements and smooth, undulating strictures of the common bile duct. Some small stones drained off after papillotomy. Just like six years ago the patient developed fever after biliary lavage but it disappeared as a result of antibiotic treatment. During the following year he was asymptomatic but serum liver tests indicating cholestasis persisted. Subsequently, an endoprosthesis was placed in the common bile duct for a period of 8 weeks. Six months later, he was asymptomatic and the serum liver tests had normalized.

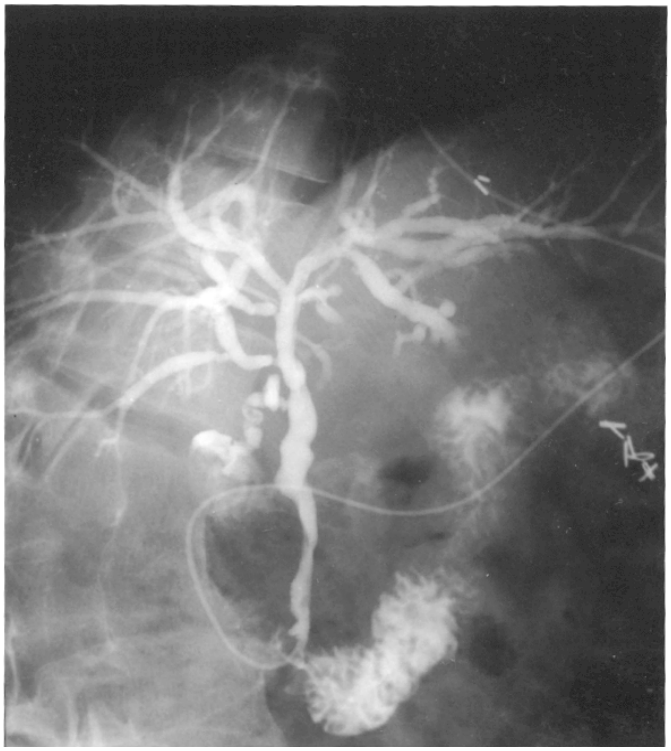

Figure 2. Patient A; cholangiography using nasobiliary dain.

Patient B, a 45-year-old male with a history of cholecystectomy for cholelithiasis and pancreatojejunostomy for chronic pancreatitis, was found by ultrasonography to have portal vein thrombosis with cavernomatous transformation. Because of recurrent pancreatitis two years later, an ERCP was performed; smooth, undulating strictures of the common bile duct, consistent with venous impressions, were demonstrated (Fig 3). One year later he complained of upper abdominal pain; laboratory examination showed cholestasis (Table I). ERCP demonstrated smooth narrowing of the distal common bile duct, consistent with external compression, and slight bile duct dilatation with small calibre changes in the proximal part. A stent was placed endoscopically. Because of cholangitis due to stent clogging the endoprothesis had to be replaced on four occasions during a period of 6 months. An attempt to create a surgical biliodigestive anastomosis failed because of the presence of multiple venous collaterals. Subsequently, two sessions of endoscopic balloon-dilatation of the distal common bile duct were performed but the serum liver tests did not improve. It is not clear whether this was caused primarily by compression of the distal common bile duct due to enlargement of the pancreatic head or biliary abnormalities secondary to the portal cavernoma. Perhaps a combination of the two factors is responsible. Recently, a metal ‘self-expandable’ endoprosthesis was placed in the distal common bile duct.

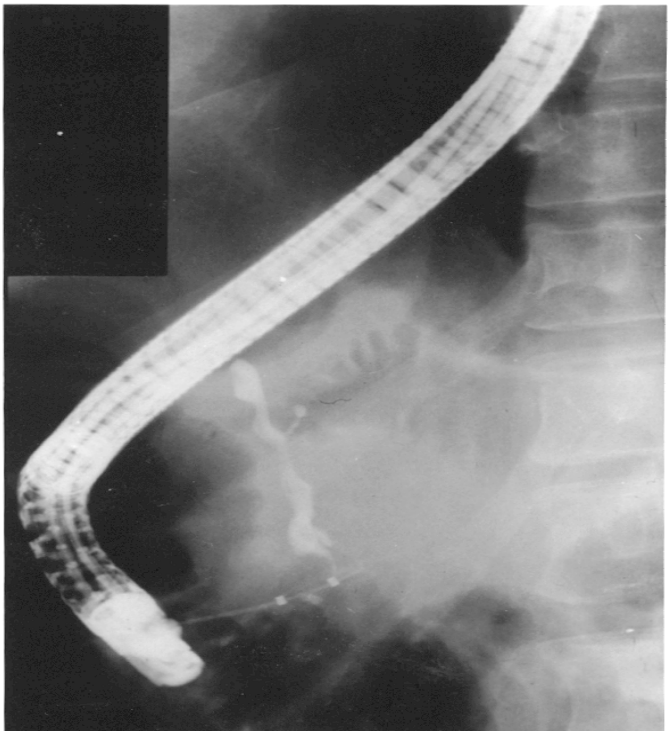

Figure 3. ERCP showing smooth, undulating strictures of the common bile duct.

Patient C, a 22-year-old female, presented with biliary colic-like pain and vomiting. Her medical history had been remarkable; the following diagnoses had been established: 'polyartritis nodosa', 'recurrent pericarditis', 'superior vena cava syndrome due to mediastinal lymphadenopathy', 'agenesis of the intrahepatic part of the inferior vena cava' and 'multiple oesophageal and gastric variceal haemorrhages due to thrombosis of the portal, splenic and superior mesenteric veins. In contrast to previous investigations, laboratory examination showed hyperbilirubinaemia (Table I). At ultrasonography multiple venous collaterals surrounding the common bile duct were seen. ERCP showed a smooth, flexible narrowing in the distal common bile duct, consistent with compression by collaterals. The signs and symptoms disappeared spontaneously and did not recur within the next four years.

Patient D, a 31-year-old male, had always been healthy until he was admitted with abdominal pain, fever and an infiltrate in the right quadrant 9 years ago. Laboratory examination showed, in addition to an elevated erythrocyte sedimentation rate of 75 mm/hour and leucocytosis of $24.9x10^9$ /l, liver abnormalities indicative of cholestasis (table 1). Blood cultures were positive for streptococci. Ultrasonography showed portal vein thrombosis with a portal cavernoma. ERCP demonstrated biliary abnormalities comparable to those seen in patients A and B (Fig 2, 3). Despite extensive investigations no explanation for this clinical picture was found. The patient recovered spontaneously and the serum liver tests normalized within a period of 6

months. Two years later he presented with symptoms of acute appendicitis. At laparotomy a retrocaecal inflamed appendix with adhesions to surrounding structures was found. Microscopical examination of the excised appendix showed appendicitis with perforation and peritonitis. The patient remained asymptomatic for the next 9 years. Retrospectively, it seems plausible that the first period of abdominal symptoms and septicaemia was probably also the result of appendicitis. The septicaemia may have caused thrombosis of the portal vein and, subsequently, the bile duct lesions.

Table 1
Serum liver tests in the 4 patients with portal biliopathy at the time of diagnosis.

	upper limit of normal	patient			
		A	B	C	D
Total bilirubin	17 µmol/l	149	90	28	10
Alkaline phosphatase	117 U/l	413	2765	64	908
γ-glutamyltranspeptidase	49 U/l	322	627	29	512
Aspartate aminotranspherase	37 U/l	127	211	15	26
Alanine aminotranspherase	41 U/l	253	197	10	75

DISCUSSION

Portal hypertension secondary to biliary liver diseases, such as primary biliary cirrhosis and primary sclerosing cholangitis, is a well-known, frequently occurring finding. In contrast, biliary abnormalities resulting from (formation of venous collaterals in) portal hypertension are rare and relatively unknown. The patients had portal vein thrombosis in all published cases.
Bile duct lesions in portal vein thrombosis, also called ‘portal biliopathy’ (6), is rarely seen in the western world since the prevalence of portal vein thrombosis is low (1). In contrast, in Asian countries such as India, portal vein thrombosis is much more common and is one of the most important causes of portal hypertension (7). The reason for this considerable difference in prevalence is unknown. In more than 90% of cases in an Indian study, a cause could not be found (8). Cholangiographical studies show that biliary abnormalities are often present (80-100%) in these patients (8-10). The vast majority of these patients remain asymptomatic. Mild to moderate elevations of serum bilirubin, alkaline phosphatase and transaminase levels are often found (9, 10). However, severe complications, such as cholestatic jaundice, cholangitis, abdominal pain (6, 11, 12) and secondary biliary cirrhosis (11), can occur and may even be the first manifestation of portal vein thrombosis (10, 11). As demonstrated by the course of disease in some of our cases, cholestasis may be transient. This could result from the passage of

biliary sludge or concrements that were caused by the biliary strictures. Other possible explanations could be that biliary compression decreases over time due to the development of new venous collaterals elsewhere or due to initial other problems, such as septicaemia as in patient D.

Two, not mutually exclusive, explanations for the pathogenesis of this disorder have been suggested in literature. In portal vein thrombosis portoportal collaterals may develop around the occluded part of the vein; this phenomenon can be considered a natural adaptation and by-pass mechanism aimed at the maintenance of portal perfusion of the liver and reduction of the venous pressure in the venous splanchnic compartment. Collaterals that surround the bile ducts may lead to bile duct compression (8, 13). The second hypothesis is that thrombosis also occurs in the efferent veins and afferent arteries of the biliary tree during thrombotic occlusion of the portal vein. This might lead to ischaemic damage to the biliary ducts with subsequent development of fibrosis and strictures (10, 11).

Imaging studies may show involvement of the entire biliary tree, but the abnormalities are usually limited to the common and left hepatic bile ducts (8, 10). Smooth, undulating narrowing is seen in the most characteristic cases. Strictures, segmental dilatation, irregularities of the bile duct wall, pruning of intrahepatic bile ducts (8, 10) and concrements (6, 8, 11) sometimes in combination with calcification of the portal cavernoma (12) can also be found. The abnormalities may mimic the ones that can be found in primary sclerosing cholangitis or cholangiocarcinoma (10, 14). Therefore, the terms ‘pseudo-sclerosing cholangitis’ or pseudo-cholangiocarcinoma’ (9) has been used to describe the abnormalities. The biliary lesions in portal biliopathy can be distinguished in particular from the abnormalities in primary sclerosing cholangitis by the smoother, undulating narrowing of the biliary lumen (8, 10). Sometimes it is possible to visualize the collaterals in the wall of the bile duct by means of ultrasonography (Fig 4).

Experience with the therapeutic possibilities for this disorder is limited. The construction of a surgical shunt, presumably the most rational approach, may result in complete disappearance of the biliary abnormalities (11, 15 -17). Technically, however, this is not always feasible. If other veins, in addition to the portal vein, are also occluded, shunt surgery may be impossible. Finally, biliary abnormalities can persist after the construction of a shunt. This could be an argument for the hypothesis that some patients have fixed (possibly ischaemic) strictures. In these cases, balloon-dilatation (10) or hepaticojejunostomy (6) may be indicated in second instance. Endoscopic placement of a stent (12-14, 18) or balloon-dilatation (11) may be successful, with or without additional extraction of biliary stones (15). One should be aware of the problems and dangers of a surgical approach. Surgical exploration of the hepatoduodenal ligament and identification of the bile ducts can be associated with significant blood loss due to

extensive vascularisation (12), sometimes with a fatal outcome (6). If biliary tract surgery is considered, this should preferably be performed after portal decompression (6).

Portal biliopathy should be included in the differential diagnosis for patients with portal vein thrombosis and cholestasis. A non-intervention policy seems justified for asymptomatic patients. For symptomatic patients, surgical or endoscopical treatment may be chosen, depending on the extent of the thrombosis and the type of the biliary lesions.

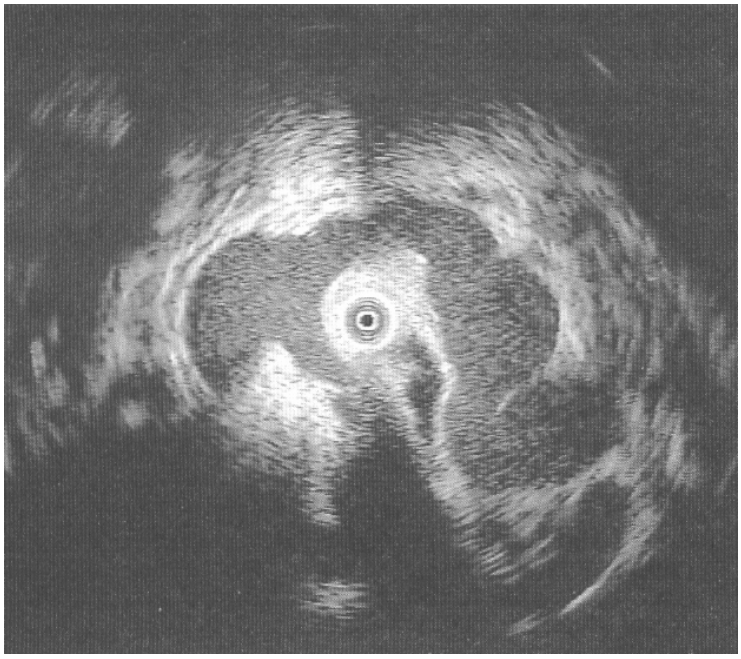

Figure 4. Intraluminal ultrasonography within the common bile duct showing venous collaterals adjacent to the bile duct wall.

Table 2
Most important causes of biliary strictures (19)

Primary sclerosing cholangitis
Ischaemia of bile ducts
Previous biliary surgery
‘graft-versus-host’ disease
Rejection of liver transplant
Infusion of cytotoxic medication in the hepatic artery
Cholangiocarcinoma
Choledocholithiasis
AIDS-related cholangiopathy
Sclerosing pancreato-cholangitis (20)
Portal vein thrombosis

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10

ENDOSCOPIC SCLEROTHERAPY FOR BLEEDING OESOPHAGOGASTRIC VARICES SECONDARY TO EXTRAHEPATIC PORTAL VEIN OBSTRUCTION IN AN ADULT CAUCASIAN POPULATION

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ABSTRACT

Background: The efficacy of endoscopic sclerotherapy for bleeding oesophagogastric varices secondary to extrahepatic portal vein obstruction in adult Caucasian patients is poorly documented.

Objective: To assess the results of endoscopic sclerotherapy for all patients with this condition who have been treated and followed in our hospital since 1982.

Design: Prospective cohort study.

Results: Twenty-one consecutive patients were included and followed during a mean period of 79 months (range 6 - 162 months). Active bleeding, encountered in five patients, was controlled by sclerotherapy in all cases. Two patients received a porto-systemic shunt after initial sclerotherapy. In all but one of the remaining 19 cases sclerotherapy resulted in eradication of the varices. The mean bleeding risk after initiation of sclerotherapy was 0.02 bleed/month/patient, which was lower than the estimated 0.13 bleed/month/patient prior to sclerotherapy. The actuarial rate of rebleeding at 5 years due to all causes and due to oesophagogastric varices was 35% and 28%, respectively. Two patients died, both from a hematological (pre-)malignancy. Actuarial 5-year survival was 95%.

Conclusions: The results of this study are in agreement with findings for pediatric and Asian patient populations and support sclerotherapy as the primary treatment modality for oesophagogastric variceal bleeding in adult Western patients with portal vein thrombosis. Life expectancy for patients with this condition is determined by the underlying cause of the portal venous obstruction.

INTRODUCTION

In Asian countries extrahepatic portal vein obstruction (EHPVO) is a frequent cause of oesophagogastric variceal bleeding, with a reported association of nearly 50% in India (1). In contrast, in Western countries EHPVO accounts for only 5-10% of variceal haemorrhages (2,3).

The efficacy of endoscopic sclerotherapy for this condition, which has been assessed mainly for children and non-Caucasian populations (4-9), is poorly documented for other populations (10,11). In this study we evaluated our experience with endoscopic sclerotherapy as the primary therapeutic modality for Western adult patients with variceal bleeding and EHPVO.

PATIENTS AND METHODS

In 1982 our hospital decided to use endoscopic sclerotherapy (ES) as the primary therapeutic modality for patients with oesophagogastric variceal haemorrhage secondary to EHPVO. In this study all 21 consecutive adults with this condition who were admitted between January 1982 and August 1996 were reviewed. The main patient characteristics are presented in table 1. EHPVO was demonstrated by means of angiography or ultrasound examination in all cases. Histology was normal for the twelve patients who underwent a liver biopsy. In the remaining 9 patients clinical, biochemical and radiological examinations showed no evidence for cirrhosis. Serum bilirubin, albumin and prothrombin time, which were frequently found to be abnormal immediately following an episode of haemorrhage, were consistently normal in all cases during follow-up. Twelve patients had previously received some form of therapy for variceal bleeding (table 1) and in each case variceal bleeding recurred before ES was initiated in our centre.

ES was performed with flexible endoscopes. Sedation was accomplished with an iv injection of 0.075 mg midazolam/kg. Oesophageal and gastric varices were treated according to the same protocol. Ethanolamine or 2% etoxysclerol were used as sclerosing agents. Variceal bleeding not responsive to injections of sclerosing agents and marked persistent bleeding following injections were treated with additional local injections of thrombin (12). Injections were intentionally intravascular, each injected volume was a maximum of 1 ml and the total volume per session never exceeded 40 ml. The aim of injection sclerotherapy was complete variceal eradication; it was performed at weekly intervals until variceal thrombosis seemed likely. Subsequently the intervals between sessions increased to 1, 3 and 6 months, respectively, followed by annual re-assessment. Any persistent or recurrent varices were then injected until they were eradicated.

Data were obtained by review of patient charts and endoscopy files. Patient follow-up continued until August 1996 or death of the patient. Variceal bleeding (13) and rebleeding (14) were defined according to internationally accepted criteria. Kaplan-Meier curves were plotted to estimate the probability of survival and rebleeding (15).

RESULTS

The mean duration of follow-up was 79 months, range 6 - 162 months. No patients were lost to follow-up.

Age at presentation

Figure 1 illustrates the range of ages of the patients at presentation. Three patients had their first variceal haemorrhage before the age of 15; each of these patients had suffered at least

four bleeding episodes before initiatation of ES. Eleven patients (52%) were older than 45 years at the time of their first variceal haemorrhage.

Active variceal bleeding

In 5 patients active variceal bleeding was observed during endoscopy. ES was successful in achieving haemostasis in all cases.

Variceal eradication

After the initial ES two patients received a surgical shunt. In one case the policy of ES as preferred standard treatment was not followed and a distal splenorenal shunt was constructed. The other patient had a nearly fatal bleeding episode following several injections in another hospital and approximately 2 weeks after one session at our centre. At endoscopy the actual bleeding site remained obscure, but no evidence was found for bleeding from sclerotherapy induced ulcers. This patient received a mesocaval shunt for ongoing bleeding. ES resulted in eradication of oesophagogastric varices in 18 of the remaining 19 cases (95%). Eradication was achieved after a median period of 8.4 months (range 0.5 - 24) and 6 injections (range 2 - 9). Variceal eradication had not yet been accomplished in a patient who died 6 months after the initial treatment.

Recurrence of varices after eradication.

After eradication, variceal recurrence was observed in 9/18 patients, after a mean period of 16.5 months (range 1 - 73.5 months). Additional ES resulted in renewed eradication in all cases.

(Variceal) Rebleeding

Recurrent bleeding was observed in nine cases. Eight patients suffered one renewed bleeding episode from oesophagogastric (n=5) or duodenal varices (n=1) and from ES-induced oesophageal ulceration (n=2). One patient suffered a total of four haemorrhages from apparently normal gastric mucosa on three occasions after ES seemed to have resulted in disappearance of gastric varices and from oesophageal ulceration. In this intriguing patient thrombosis of all major splanchnic veins and complete obstruction of the inferior and superior vena cava were found.

Most episodes of rebleeding were observed early after the initiation of ES: five patients haemorrhaged again before eradication of varices was achieved and within 2 months of the first injection. Two patients experienced recurrent oesophageal variceal bleeding after 1 year. The actuarial 5-year rate of rebleeding due to all causes and due to oesophagogastric varices was 35% and 28%, respectively (figure 2).

Estimated variceal bleeding rate prior to and following ES

For nine patients sufficient data were available to determine the moment of development of EHPVO. For these patients the bleeding rate prior to and following ES treatment was calculated. Prior to ES, 30 variceal bleeding episodes occurred during 1615 months; the calculated incidence was one variceal haemorrhage every 54 months or a mean incidence of 0.13 bleeds/month/patient. In 843 months after the initiation of ES three bleeding episodes were observed; the calculated incidence was one variceal haemorrhage every 281 months or a mean incidence of 0.02 bleeds/month/patient.

Survival

The 5-year actuarial survival rate was 95% (figure 3). There were two deaths during the 14-year study period: one due to post-splenectomy complications in a patient with chronic myeloid leukaemia 6 months after initial ES and one due to septicemia in a patient with polycythemia vera 5 years after initial ES.

Complications of ES

A total of 179 ES procedures led to complications in 5 cases (24%). Symptomatic oesophageal stenosis developed in two patients who successfully underwent endoscopic dilatation. Bleeding from oesophageal ulcers, caused by previous sclerotherapy, was observed in three patients. Asymptomatic oesophageal ulcers following ES were not regarded as complications.

DISCUSSION

The results of this study indicate that variceal bleeding in adult patients with portal vein thrombosis can be managed successfully with endoscopic sclerotherapy. Active bleeding was controlled in all cases and there was no mortality associated with variceal rebleeding or complications. The observed rate of variceal rebleeding at one year was 20 %, which is substantially lower than the 50 % reported for patients with cirrhosis (16). During long-term follow-up recurrent variceal bleeding was rare, indicating that in this condition prolonged variceal eradication is feasible and is associated with virtually complete protection against rebleeding. The ultimate prognosis was determined by the underlying cause of the portal vein obstruction; during a mean follow-up of 79 months no mortality related to portal hypertension or to non-malignant underlying disorders was observed.

Some aspects of the present study warrant discussion. Although we carefully included all consecutive cases with EHPVO and variceal bleeding treated during a 14 year period, the number of patients is small. Furthermore, two of the 21 patients (10%) received a

portosystemic shunt after initial ES, and the subsequent course was favourable in both cases. Finally, our hospital is a tertiary referral centre and selection bias may have resulted in under- or over-representation of certain patient categories.

Most previously published studies of ES for bleeding varices secondary to EHPVO involved pediatric patients (4-7). These studies uniformly demonstrated gratifying results and, on the basis of their experience, all authors advocated ES as the therapy-of-choice for this condition. Remarkably few studies of adult, and especially Western, patients have been performed. Thatcher et al. from Cleveland reported on their results with ES for eight (seven adult or teenaged) patients with EHPVO (10). During a mean follow-up period of 24 months they observed 3 patients with rebleeding. ES was associated with decreased transfusion requirements. Kahn et al. published their extensive, 15-year experience with ES in Cape Town where they treated 55 adult and teenaged patients with EHPVO (11). Eradication of oesophageal varices was achieved in 80% of cases. Eleven patients suffered a total of 18 renewed haemorrhages before variceal eradication and six patients haemorrhaged again on seven occasions after variceal obliteration. Four patients died: one of complications after surgery to control variceal bleeding, one of a ruptured splenic vein and two of a cardiac cause not related to portal hypertension. Neither report contains information on the ethnic composition of the patient group, and the South African patients in particular may have differed from our group of West European white patients. In addition, our patients were considerably older - mean age 48 years - than those treated by Thatcher (mean: 22 years) and Kahn et al (mean: 30 years). It is noteworthy that half of our patients were over 45 years of age at the time of presentation, confirming that in Western countries variceal bleeding associated with EHPVO can be encountered in patients of any age (17).

Controversy and uncertainty exist with regard to the optimum therapy for patients with EHPVO and variceal bleeding. Unfortunately, a preference for endoscopic or surgical therapy cannot be based on the results of randomized controlled investigations. Favourable results of surgical therapy, mainly for children and young adults, have been reported by several groups (18-20). Warren et al, who treated 25 adult patients surgically, i.e. selective distal splenorenal shunts in most cases (21), reported absence of surgical mortality and rebleeding in only 3 cases. In six cases shunt stenosis required dilatation after 3-6 months. These 25 patients came from a total group of 70 patients with EHPVO and a history of bleeding varices and therefore constituted a highly selected group. The outcome of surgical intervention for other patients, many of whom had undergone previous operations, was poor.

Orozco et al. performed the Sugiura procedure (paraoesophagogastric devascularization, oesophageal transection, splenectomy, vagotomy and pyloroplasty) (22) on 27, mainly teenaged or adult, patients. Recurrent bleeding was observed in only two cases. However,

since there was one surgical mortality and serious post-operative complications occurred in eight patients, this procedure seems unattractive as therapy of first choice.

Our data highlight the problems associated with shunt surgery for patients with portal venous obstruction: in nearly half of our cases the thrombotic occlusion also involved the splenic and superior mesenteric veins; in 3 patients previously created shunts were unsuccessful and at least one-third of cases were at high-risk for thrombosis (and hence for shunt occlusion). Currently, most available data seem to support ES as the primary therapy for variceal bleeding secondary to EHPVO in both pediatric and adult patients. It has now been demonstrated convincingly that variceal band ligation is superior to ES for patients with cirrhosis (23). It seems likely that this will also apply for patients with EHPVO. Surgical therapy can probably best be reserved for patients who do not respond favorably to endoscopic treatment or who cannot undergo endoscopic treatment for other reasons (2,3,24).

In conclusion, endoscopic injection sclerotherapy is effective and safe for managing variceal bleeding in adult West European patients with EHPVO. In general, life expectancy for these patients is excellent and mortality seems mainly to be determined by the presence of underlying (pre-) malignant conditions.

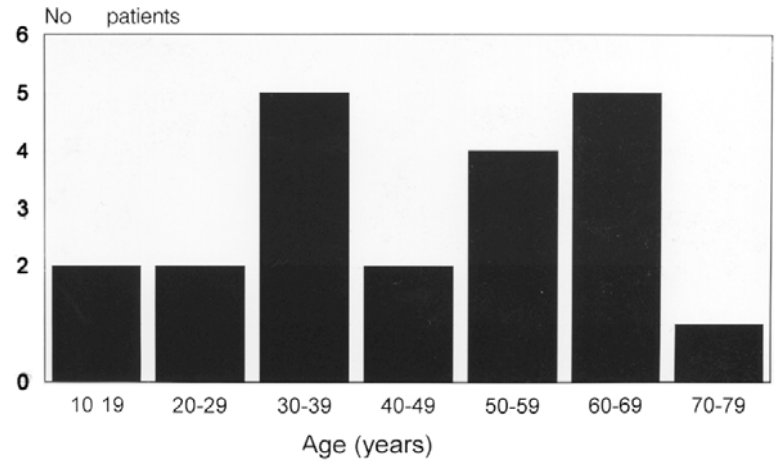

Figure 1

Range of ages of the patients at initial ES in our hospital.

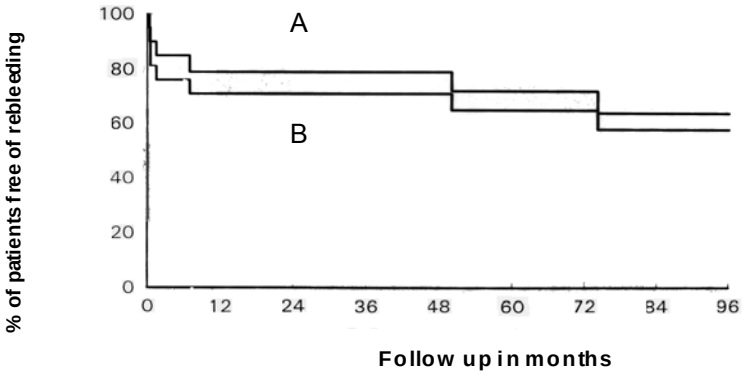

Figure 2

Kaplan-Meier curve showing the percentage patients free of:

a: oesophagogastric variceal rebleeding

b: rebleeding from all causes.

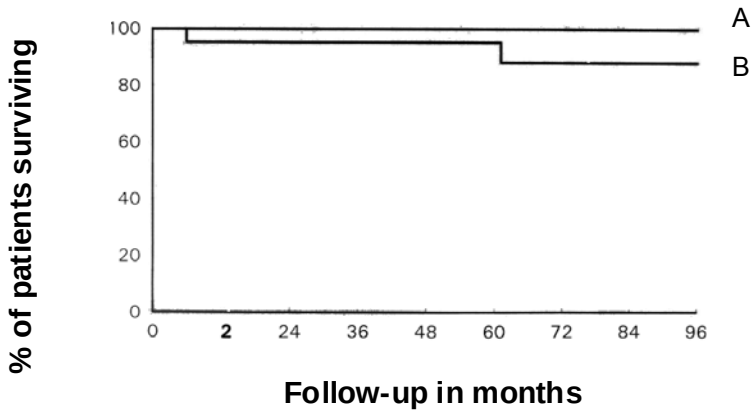

Figure 3

Kaplan-Meier curve showing the percentage patients dying from:

a: variceal bleeding

b: all causes.

Table 1

Clinical features of patients with EHPVO

Age: median; range (yr)	48; 16-74
Sex (M/F)	7/14
Variceal grade I/II/III/IV (no of patients)*	1/2/8/9
Gastric varices (no of patients)	14
Etiology of EHPVO (no of patients)	
- protein S deficiency	2
- myelofibrosis	2
- polycythemia vera	1
- chronic myeloid leukaemia	1
- umbilical vein thrombosis	2
- resection of portal vein (pancreatic carc.)	1
- peritonitis/appendicitis	1
- cryptogenic	11
Extent of venous obstruction (no of patients)*	
- portal vein	8
- portal and superior mesenteric vein	3
- portal, superior mesenteric and splenic vein	8
- portal, splenic, superior and inferior mesenteric vein	1
Previous treatment (no of patients)	
- splenectomy	3
- surgical shunt	3
- propranolol	1
- endoscopic sclerotherapy (other clinic)	5
- conservative	6

* not documented in one patient

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SUMMARY AND DISCUSSION

Chapter 1 provides a general introduction to this thesis. Relevant aspects of anatomy and pathophysiology of portal hypertension are reviewed, emphasizing the concepts of collateral and hyperdynamic circulation.

Chapter 2 shows the results of a study evaluating the value of a barium swallow for diagnosing oesophageal varices. We found that this simple radiological method allows diagnosis of varices with acceptable reliability. Barium swallow could be used when endoscopy is ill tolerated or not acceptable to the patient. However, endoscopy is, and will remain, the standard diagnostic method. The disadvantage of more subjective interpretation is counterbalanced by providing additional information on the color and other variceal characteristics as well as on other lesions in the upper gi-tract, including the presence of gastric varices and portal hypertensive gastropathy.

Chapter 3 suggests that the well-known NIEC system for assessing the risk for variceal bleeding can be further improved by a number of modifications. These results may of interest particularly from a scientific point of view. This study also confirms that variceal size, the presence of local variceal abnormalities (‘red spots’) and the degree of liver insufficiency have prognostic significance for the prediction of a first variceal bleeding episode.

Chapter 4 reports the results of a multicenter randomized controlled trial evaluating endoscopic sclerotherapy for the primary prevention of variceal bleeding. The main findings were that sclerotherapy did not improve the risk of variceal bleeding or mortality. However, death directly attributable to variceal bleeding was significantly lower in patients receiving prophylaxis as compared to controls. Also given the results of comparable studies, we do not recommend prophylactic sclerotherapy. Variceal band ligation has a number of clear advantages over sclerotherapy and may be considered for primary prophylaxis, particularly in high-risk patients and those patients who do not tolerate or respond to propranolol, the currently recommended first-line prophylactic treatment.

Chapter 5 describes our experience with the use of thrombin as an injecting agent for treating active variceal bleeding. This study confirmed clinical impression that thrombin is highly effective in arresting bleeding, while no evidence was found for adverse effects. Unfortunately, thrombin is no longer commercially available. Currently available data suggest that intravenous administration of recombinant factor VIIa may be a highly effective alternative for treating active variceal haemorrhage as well as bleeding of other origin.

Interestingly, recombinant factor VIIa results in the generation of high concentrations of thrombin at the site of bleeding.

Chapter 6. In a small randomized controlled trial TIPS was compared with endoscopic variceal band ligation in patients with a first or second episode of variceal bleeding. As expected, the incidence of rebleeding was significantly lower after TIPS, but this was not associated with improved survival. TIPS increased the risk of encephalopathy and the costs of this treatment were estimated to be higher. These results are in agreement with the findings of most other studies and suggest that TIPS is not a first-line therapeutic modality in the secondary prophylaxis of variceal bleeding. TIPS, however, may have advantages in particular patients groups such as patients with gastric varices or with other complications of portal hypertension, and this possibility clearly should be addressed by additional studies.

Chapter 7 reports the experience obtained with TIPS in the University Hospital Rotterdam in a cohort of 82 patients with variceal bleeding, refractory ascites and other complications of portal hypertension, followed for 3-9 years. The main finding was that with regular surveillance and re-interventions when indicated the definitive loss of shunt function was 17% at 5 years. Non-alcoholic etiology and increasing platelet counts were predictive for developing shunt insufficiency. For patients with variceal bleeding the 1 and 4 year rate of recurrent variceal bleeding was 21% and 27%, respectively. Recurrent bleeding was caused by shunt dysfunction and persistent portal perfusion of collaterals. TIPS was found to be beneficial for a relative small percentage of patients with refractory ascites; mortality in this group was 43% at 6 months. The overall risk for developing encephalopathy was 52% at 3 years. Chronic or severe intermittent encephalopathy was observed for 20% of the patients after 3 years; age and serum creatinine were independent risk factors. Overall survival was 61% at 1 year and 42% at 5 years; age, serum albumin and creatinine were independent risk factors for mortality.

Chapter 8. Ectopic varices are defined as portal-systemic collaterals occurring anywhere outside the gastro-oesophageal junction. Bleeding from these varices is a rare complication of portal hypertension. In this chapter we report our experience with 22 patients over an eighteen-year period, the largest reported series. We found that in the majority of patients local therapies, e.g. sclerotherapy, surgical sutures or reinsertion of enterostomies, fail to provide long-term control of bleeding and that a portal-pressure lowering procedure, TIPS or a surgical shunt, seems more effective. Therefore, a shunt procedure should at least be considered early in the course of patients presenting with bleeding from varices at ectopic sites.

Chapter 9 shows the results of another retrospective study with long-term follow-up evaluating the efficacy of endoscopic sclerotherapy for variceal bleeding in patients with portal vein thrombosis, a rather infrequent condition in the Western world. The results of this study are in agreement with findings for pediatric and Asian populations. The observed rate of rebleeding (28% at 5 years) and the fact that mortality from variceal bleeding was not observed, supports endoscopic therapy as the primary treatment option for variceal bleeding in this condition. This study confirms that life expectancy for patients with portal vein thrombosis is determined by the underlying cause.

Chapter 10 is dealing with portal biliopathy, a characteristic biliary complication of portal vein thrombosis. We report our experience and discuss the pathophysiology and therapeutic options of this unfamiliar condition. The clinical course of patients with bile duct strictures due to compression by collaterals may vary from a asymptomatic state to development of obstructive jaundice, severe infectious complications and secondary biliary cirrhosis. In general, for symptomatic cases endoscopic treatment seems the therapy of choice, but portal-systemic shunt surgery may be required in a subgroup of patients.

SAMENVATTING EN DISCUSSIE

Hoofdstuk 1 geeft een algemene inleiding tot dit proefschrift. Relevante aspecten van de anatomie en pathophysiologie van portale hypertensie worden kort behandeld, met een nadruk op de begrippen collaterale circulatie en hyperdynamische circulatie.

Hoofdstuk 2 toont de resultaten van een studie naar de waarde van röntgenologisch barium contrastonderzoek bij de diagnostiek van oesophagusvarices. Wij vonden dat met deze simpele radiologische onderzoeksmethode varices met acceptabele betrouwbaarheid kunnen worden vastgesteld. Dit onderzoek kan gebruikt worden wanneer endoscopisch onderzoek slecht verdragen wordt of niet acceptabel is voor de patiënt. Wij menen evenwel dat endoscopische diagnostiek de standaard diagnostische methode is en ook zal blijven. Het nadeel hierbij van een meer subjectieve interpretatie wordt gecompenseerd door het feit dat endoscopie niet alleen aanvullende informatie verschaft over de kleur en andere karakteristieken van varices, maar ook over andere afwijkingen in de bovenste tractus digestivus, zoals maagvarices en congestieve gastropathie.

Hoofdstuk 3 suggereert dat het bekende NIEC systeem voor het bepalen van het risico van het krijgen van een varicesbloeding door een aantal modificaties verbeterd kon worden. Deze bevindingen lijken vooral vanuit wetenschappelijk perspectief interessant. Deze studie bevestigde dat de grootte van de varices, de aanwezigheid van lokale wandafwijkingen (‘red spots’) van de varices en de mate van leverinsufficiëntie prognostische betekenis hebben ten aanzien van het optreden van een eerste varicesbloeding.

Hoofdstuk 4 toont de resultaten van een multicentrische gerandomiseerde trial betreffende endoscopische sclerotherapie bij de primaire preventie van varicesbloedingen. De belangrijkste bevinding was dat sclerotherapie niet leidde tot een lagere incidentie van varicesbloedingen of sterfte. De mortaliteit direct samenhangend met varicesbloedingen bleek evenwel significant lager in de groep profylactisch behandelde patiënten. Mede gelet op de resultaten van soortgelijke studies kan sclerotherapie voor de profylaxe van varicesbloedingen niet worden aanbevolen. Varices bandligatie heeft een aantal voordelen ten opzichte van sclerotherapie en zou kunnen worden overwogen bij de primaire preventie van bloedingen, met name wanneer er sprake is van hoogrisico patiënten of wanneer behandeling met propranolol, de huidige profylactische standaard therapie, niet wordt verdragen of ineffectief blijkt.

Hoofdstuk 5 beschrijft onze ervaring met het gebruik van thrombine bij injectietherapie voor acute varicesbloedingen. Deze studie bevestigde de bestaande klinische impressie dat thrombine zeer effectief is bij het tot staan brengen van bloedingen, terwijl geen aanwijzingen werden gevonden voor bijwerkingen. Helaas is thrombine niet langer commercieel verkrijgbaar. Thans beschikbare gegevens suggereren dat intraveneuze toediening van recombinant factor VIIa zeer effectief zou kunnen zijn bij de behandeling van actieve varicesbloedingen en bloedingen van andere origine. Het is interessant dat toediening van recombinant factor VIIa hoge concentraties thrombine genereert ter plaatse van bloedingen.

Hoofdstuk 6. In een gerandomiseerde gecontroleerde trial werd behandeling met TIPS vergeleken met endoscopische bandligatie bij patiënten met een eerste of tweede varicesbloeding. Niet onverwacht bleek de incidentie van recidief bloedingen significant lager na TIPS behandeling, maar dit ging niet gepaard met een verbeterde overleving. TIPS verhoogde de kans op ontwikkeling van encephalopathie en de kosten van deze behandeling waren hoger. Deze resultaten zijn in overeenstemming met die van de meeste vergelijkbare studies en suggereren dat TIPS geen eerstelijns behandelingskeus is bij de secundaire preventie van varicesbloedingen. TIPS zou evenwel belangrijke voordelen kunnen hebben bij bepaalde patiëntengroepen zoals patiënten met maagvaricesbloedingen of andere complicaties van portale hypertensie, en deze mogelijkheid verdient nadrukkelijk nadere bestudering.

Hoofdstuk 7 beschrijft de ervaring met TIPS in het Academisch Ziekenhuis Rotterdam bij 82 patiënten met varicesbloedingen, refractaire ascites en andere complicaties van portale hypertensie, die gedurende 3-9 jaar vervolgd werden. De belangrijkste bevinding was dat met reguliere surveillance en re-interventies wanneer geïndiceerd het definitieve verlies van shunt functie 17% was na 5 jaar. Een niet alcoholische etiologie van de leverziekte en hogere trombocyten waarden bleken voorspellend t.a.v. het ontwikkelen van shuntinsufficiëntie. Voor patiënten met varicesbloedingen was de kans op recidief (varices)bloedingen na 1 jaar 21% en an 4 jaar 27%. Recidief bloedingen werden veroorzaakt door shunt dysfunctie en door persisterende doorbloeding van collateralen. Een relatief klein deel van de patiënten met refractaire ascites had baat bij behandeling met TIPS; de mortaliteit in deze groep was 43% na 6 maanden. De kans op het ontwikkelen van encefalopathie was 52% na 3 jaar. Chronische of intermitterend optredende ernstige encefalopathie werd waargenomen bij 20% van de patiënten na 3 jaar; leeftijd en het serum creatinine bleken onafhankelijke risicofactoren. De overleving voor de gehele groep was 61%

na 1 jaar en 42% na 5 jaar; leeftijd, serum albumine en serum creatinine waren onafhankelijke risicofactoren voor sterfte.

Hoofdstuk 8. Ectopische varices kunnen gedefinieerd worden als porto-systemische collateralen voorkomend buiten het gastro-oesophageale overgangsgebied. Bloedingen uit deze varices zijn een zeldzaam voorkomende complicatie bij portale hypertensie. In dit hoofdstuk worden onze ervaringen beschreven bij 22 patiënten die gedurende een periode van 18 jaar werden gezien, waarmee dit de grootste gerapporteerde serie is. Wij stelden vast dat lokale behandelingen als sclerotherapie, chirurgische doorstekingen of het verplaatsen van een enterostoma, vaak onvoldoende zijn om recidief bloedingen te voorkomen en een ingreep die de portale druk verlaagt, TIPS of een chirurgische shunt, effectiever is. Daarom moet een shunt procedure vroeg in het beloop bij alle patiënten die zich presenteren met een ectopische varicesbloeding tenminste worden overwogen.

Hoofdstuk 9 toont de resultaten van een andere retrospectieve studie met lange follow-up duur naar de effectiviteit van endoscopische sclerotherapie voor varicesbloedingen bij patiënten met een vena portae thrombose, een relatief weinig voorkomende aandoening in de Westerse wereld. De resultaten van deze studie zijn in overeenstemming met die van studies bij paediatrische en Aziatische populaties. De waargenomen kans op recidiveren van de bloeding (28% na 5 jaar) en het feit dat sterfte ten gevolge van varicesbloedingen niet werd waargenomen, ondersteunen de positionering van endoscopische sclerotherapie als de eerste lijnsbehandeling voor varicesbloedingen bij deze aandoening. Deze studie bevestigt dat de levensverwachting van patiënten met vena portae thrombose bepaald wordt door de aard van de onderliggende aandoening.

Hoofdstuk 10 betreft portale biliopathie, een karakteristieke biliaire complicatie bij vena portae thrombose. Wij beschrijven onze ervaring en bespreken de pathophysiologie en therapeutische opties bij deze weinig bekende aandoening. Het klinisch beloop bij patiënten met biliaire stricturen ten gevolge van compressie door collateralen kan variëren van geheel asymptomatisch tot het ontstaan van obstructie icterus, ernstige infectieuze complicaties en ontwikkeling van secundaire biliaire cirrose. In de meeste gevallen lijkt endoscopische behandeling de therapie van keus, bij een deel van de patiënten kan het aanleggen van een porto-systemische shunt noodzakelijk zijn.

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CURRICULUM VITAE

De auteur van dit proefschrift werd geboren op 19 oktober 1952 te Krimpen a/d IJssel. Na het behalen van het einddiploma HBS-B aan het Rotterdams Lyceum in 1971 studeerde hij Geneeskunde aan de Rijksuniversiteit Leiden en behaalde het artsdiploma in 1977. Tijdens het vervullen van de militaire dienstplicht was hij gedetacheerd in het Militair Hospitaal 'Dr. A. Mathijssen' te Utrecht en volgde aldaar het eerste jaar van de opleiding tot internist (opleider dr. C.J. van Belle). Deze opleiding werd vervolgens voortgezet in het St. Elisabeth Ziekenhuis te Leiderdorp (opleider: dr. W.J. van Amstel) en vanaf 1979 in het Bergweg Ziekenhuis te Rotterdam op de afdeling van dr. J. Silberbusch (opleider: dr. G.J.H. den Ottolander). In 1982 werd hij ingeschreven in het specialistenregister als internist. Vanaf 1984 was hij als internist/onderzoeksarts en vanaf 1988 als staflid werkzaam in het Academisch Ziekenhuis Rotterdam, eerst op de afdeling Interne Geneeskunde II (hoofd prof. J.H.P. Wilson) en sinds 1998 tot heden op de afdeling Maag,- Darm-, en Leverziekten (hoofd ad interim prof. dr. S.W. Schalm, vanaf augustus 2000 hoofd prof. dr. E.J. Kuipers). Hij volgde de specialisatie tot maag-darm-leverarts onder M. van Blankenstein en werd in 1995 ingeschreven in het desbetreffende register. Vanaf 1984 werden studies op het gebied van portale hypertensie verricht onder supervisie van en in nauwe samenwerking met prof. dr. S.W. Schalm. Vanaf 1990 was hij daarnaast intensief betrokken bij het opzetten en uitvoeren van, deels landelijke, studies betreffende de cholestatische leverziekten Primaire Biliaire Cirrhose en Primaire Scleroserende Cholangitis. Hij is gehuwd met Anneke en heeft twee kinderen, Marlies en Thomas.

DIAGNOSTIC AND THERAPEUTIC GUIDELINES FOR BLEEDING FROM OESOPHAGEAL, GASTRIC AND ECTOPIC VARICES.

Pre-primary prophylaxis (prevention of development) of varices

1. In patients with liver disease therapeutic efforts to prevent the development of portal hypertension and varices are essential. Prevention and adequate diagnosis and treatment of chronic liver disease are the cornerstones to accomplish these goals.
2. Currently, no specific treatment has been identified. Pre-primary prophylaxis with propranolol was found to be ineffective (1).

Diagnosis of varices in patients without known (large) varices

1. Diagnosis of varices is relevant considering the potential of prophylactic treatment.
2. In patients with chronic liver disease and normal platelet counts the presence of varices is unlikely (2).
3. Patients with possible portal hypertension should undergo endoscopic examination. Patients with small varices should undergo repeat endoscopy after one year (3). Patients without varices should be reinvestigated at two-year intervals, but the frequency of repeat endoscopy should take into account the etiology, activity and severity of liver disease (4).
4. Radiological examination can be used when endoscopy is not acceptable to the patient (5).
5. There is no data available regarding the policy in patients with repeated negative examinations or stable findings.

Prevention of first variceal bleeding

1. In general, aspirin and non-steroidal anti-inflammatory drugs should preferably be avoided in patients with varices since these agents may cause variceal bleeding (6).
2. There is no data whatsoever indicating that (blind) introduction of nasogastric tubes or the consumption of e.g. chicken or fish is risky in patients with varices.
3. For patients with non-cirrhotic portal hypertension no data are available to support any specific prophylactic treatment.
4. All patients with large varices should be treated (7, 8). Varices larger than grade II (scale I-IV) are considered large.
5. The first line treatment is propranolol or nadolol. The dose should be increased to achieve a 25% reduction in resting heart rate or down to 55 b.p.m. or development of symptoms (4).
6. Slow-release propranolol is recommended to improve compliance.

7. There is no consensus how to treat noncompliant patients or patients who have contraindications of intolerance to β-blockers. Available evidence does not support other pharmacological treatment (4). Prophylactic band ligation is a reasonable choice in this situation (9-11)

Acute bleeding from oesophageal and gastric varices

1. A diagnosis of oesophageal variceal bleeding can be made when active bleeding from varices or the 'white nipple' sign (fibrin plug) is observed. The diagnosis can also be established when endoscopy is performed within 24 hours of onset of haematemesis or melaena, or when blood is found in the stomach, and varices are present in the absence of other potential bleeding sources (12).
2. Endoscopy should be performed as soon as possible after admission, especially in patients with clinically significant bleeding or in patients with features suggesting cirrhosis. In mild bleeds, causing neither haemodynamic changes nor requiring blood volume restitution, endoscopy can be done electively (13).
3. Endotracheal intubation is mandatory if there is any concern about lung aspiration, particularly in patients undergoing endoscopy with ongoing or recent haematemesis, encephalopathy and circulatory instability (13).
4. In suspected variceal bleeding vasoactive drugs should be started as soon as possible. Institution of this treatment should not be delayed until diagnostic endoscopy has been performed (13).
5. Currently, there is no clear preference for terlipressin, somatostatin or octreotide. In patients confirmed to bleed from varices drug therapy can be maintained for up to 5 days (13).
6. Antibiotic prophylaxis, e.g. oral norfloxacin 2 x 400 mg/day for 10 days, is an integral part of treatment and should be instituted from admission (13, 14). Initially, intravenous antibiotics may be preferred e.g. ciprofloxacin or a cephalosporin.
7. Lactulose, e.g. 2 x 30 ml/day, should be given to prevent hepatic encephalopathy (13).
8. In acute oesophageal bleeding either band ligation or injection therapy can be used (13). Band ligation is technically more difficult than injection therapy in cases with active bleeding. Injection of tissue adhesives is particularly effective for stopping active bleeding; injection volumes should not exceed 1 ml.
9. There is no consensus on the treatment of gastric varices (8). Injection of tissue adhesives is now the endoscopic therapy of choice (15, 16). In patients with

extensive varices, inadequate endoscopic therapy or previous gastric variceal bleeding, TIPS should be sincerely considered as the therapy of choice (17, 18).

10. In patients with gastric, especially large fundus, varices, the possibility of 'left-sided' of 'segmental' portal hypertension should always be considered. In this rare condition splenectomy may be curative (19).
11. Endoscopic therapy is the treatment of choice for oesophagogastric bleeding in patients with portal vein thrombosis (20).
12. Balloon tamponade is an effective, temporary therapy for massive variceal bleeding (13).

Prevention of recurrent bleeding

1. Consensus is that either β-blockade (propranolol) or endoscopic band ligation is the first-line treatment to prevent recurrent variceal haemorrhage (21).
2. Combinations of drug treatment and endoscopic treatment have not been found to be superior (21, 22).
3. Band ligation is the preferred treatment for patients who have bled while on β-blockers (21).
4. There is no consensus on the definition of 'failed' therapy. In general, a second episode of recurrent variceal bleeding may be considered as reflecting failed therapy. For all patients with multiple episodes of variceal bleeding liver transplantation should be considered. The most appropriate therapy for patients failing on first-line therapy is TIPS, especially for patients with advanced (Child class B ore C) liver disease. For Child class A and non-cirrhotic patients a surgical shunt may also be considered (21).

Ectopic variceal bleeding

1. Ectopic variceal bleeding is rare. In patients with portal hypertension and unexplained (gastrointestinal) blood loss bleeding from ectopic varices should be considered (23, 24)
2. Previous abdominal and pelvic surgery is a main risk factor for developing ectopic varices (23).
3. Rectal bleeding in patients with portal hypertension is caused by varices, and not by haemorrhoids, until proven otherwise (23).
4. Intra-abdominal bleeding may be caused by ruptured peritoneal varices (23); urgent porto-systemic shunting is the therapy of choice.
5. Local therapies are likely to fail and a shunt procedure should be considered in patients with bleeding from ectopic varices.

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