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**ENDOSCOPIC INJECTION SCLEROTHERAPY IN THE TREATMENT  
OF BLEEDING OESOPHAGEAL VARICES IN PATIENTS WITH  
PORTAL HYPERTENSION DUE TO ALCOHOL-INDUCED  
CIRRHOSIS: AN ASSESSMENT OF ACUTE CONTROL OF  
BLEEDING, PREVENTION OF RECURRENT BLEEDING AND  
PROGNOSTIC FACTORS PREDICTING EARLY VARICEAL  
REBLEEDING AND DEATH**

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**A thesis submitted for the degree of  
MASTER OF SCIENCE (MEDICINE)  
Faculty of Health Sciences  
UNIVERSITY OF CAPE TOWN  
15 August 2009**

## DECLARATION

I, Jacobus Edmund Joubert KRIGE, hereby declare that the work on which this thesis is based is my original work (except where acknowledgements indicate otherwise) and that neither the whole work nor any part of it has been, is being, or is to be submitted for another degree in this or any other university.

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**Date of Submission:** 15 August 2009

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## CHAPTER 1

### INTRODUCTION

Variceal bleeding is the most serious complication of portal hypertension and substantially alters the natural history of patients with compensated alcoholic cirrhosis (Villanueva 2009). One-third of deaths from cirrhosis are related to portal hypertension, and are due mainly to oesophageal variceal bleeding (Garcia-Pagan 2008). Up to 30 per cent of initial variceal bleeding episodes are fatal, and as many as 70 per cent of survivors, if inadequately treated, have recurrent variceal bleeding (Kravetz 2007).

The treatment of variceal haemorrhage has evolved markedly in the past decade (Krieger 2009a, Garcia-Tsao 2008). Substantive advances have included new drug combinations (Dell'Era 2008), improved endoscopic techniques and refinements of variceal band ligation (Tait 1999, Krieger 2005, Baron 2009), the selective use of radiologically inserted transjugular intrahepatic portosystemic shunts (Boyer 2005), the recognition of the diminishing role of narrow diameter polytetrafluoroethylene interposition portacaval shunts (Rosemurgy 2005) and the exponentially increasing indications for liver transplantation (Busuttil 2008) in patients who have progressive hepatic decompensation and persistent variceal bleeding. Although these advances in treatment have reduced overall mortality (Chalasani 2003, Carbonell 2004), uncontrolled or recurrent bleeding from varices and the consequences of progressive liver failure remain the commonest causes of early death in alcoholic cirrhotic patients (Mihai 2004). The spectrum of interventions required to control variceal bleeding and achieve efficient and successful treatment of the severe and potentially life threatening complications of portal hypertension are invasive, complex and may

necessitate advanced skills. (Treiber 2005). No single modality is applicable to all patients and knowledge of the alternatives allows the well-informed surgeon to choose the appropriate therapy for each clinical situation. A co-ordinated multidisciplinary team approach is essential as each of these therapies may be required at different stages in different patients (Krige 2007b, Krige 2009a).

The ideal treatment of portal hypertension and bleeding varices should be universally effective, safe, easy to administer and inexpensive. Currently no such treatment exists and the surgeon or physician is obliged to select the most appropriate intervention from a menu of currently available therapeutic options, none of which is ideal or applicable to all patients. The rational treatment of oesophageal varices depends on a clear understanding of the risks of rebleeding and the response to each specific intervention. The selection of the correct and appropriate intervention is critical and requires a comprehensive understanding of the relative efficacy and safety of each treatment compared to other competing options. In addition, the chosen intervention requires detailed knowledge of the criteria underpinning the correct selection of patients for treatment in order to maximize the therapeutic benefits of the appropriate choice while minimising the side effects of the treatment. The optimal management of bleeding oesophageal varices therefore requires a full appreciation of portal, gastric and oesophageal venous collateral anatomy, the pathogenesis and haemodynamic consequences of variceal bleeding and the utility of each available therapy at specific stages in the natural history of portal hypertension (Henderson 1998).

Endoscopic treatment has become the principal first-line intervention in patients with bleeding oesophageal varices, both during the acute event and for long-term therapy to prevent recurrent bleeding (Kriger 2005). After control of the index bleed, there is a 70% chance of rebleeding with a similar mortality. The risk of rebleeding is greatest during the first few days after initial variceal haemorrhage (Sharara 2001). Survival after variceal bleeding depends largely on the rapidity and efficacy of initial primary haemostasis and the presence and severity of underlying liver disease and hepatic functional reserve (Kriger 2009b). Early rebleeding has been shown to be a strong predictor of mortality and recurrent variceal bleeding substantially increases the risk of complications which further contribute to mortality (Kriger 2009b), emphasizing that rapid and sustained control of variceal bleeding remains the principal imperative of endoscopic intervention (Triantos 2006). Several important clinical considerations influence the choice of therapy as well as the prognosis in individual patients. These include the natural history of the disease causing the portal hypertension, the location of the bleeding varices, residual hepatic function, the presence of associated systemic disease, continuing drug or alcohol abuse, patency of major splanchnic veins and the response to each specific treatment (Henderson 1998).

In order to address these unresolved questions, each of the three clinical studies in this thesis evaluated a specific aspect of variceal bleeding in a large cohort of alcoholic cirrhotic patients treated with endoscopic injection sclerotherapy. In the literature review, the historical perspective of the evolution of endoscopic treatment of varices, the natural history of variceal development and pathogenesis of oesophageal variceal bleeding, relevant oesophageal venous anatomy and the

technique and complications of endoscopic injection sclerotherapy of oesophageal varices were evaluated as well as a comparison of the efficacy of injection sclerotherapy in the treatment of acute bleeding oesophageal varices with alternative therapies including beta-blockers, sclerotherapy plus beta-blockers, variceal band ligation, surgical shunts and transjugular intrahepatic portosystemic shunts.

### **Study 1**

Patients who survive a first episode of variceal bleeding have a high risk of further bleeding and death. The median incidence of variceal rebleeding during the first 24 months after the index bleed in untreated controls of 20 prospective randomised controlled trials of non-surgical treatment for prevention of recurrent bleeding is in excess of 60% (D'Amico 1997). Present knowledge suggests that the risk of rebleeding is higher in Child-Pugh C patients. Although the utility of endoscopic injection sclerotherapy in controlling acute variceal bleeding has been extensively reported, the long term efficacy and safety of injection sclerotherapy in a high risk cohort such as patients with alcohol-induced cirrhosis are poorly defined and documented. Since endoscopic treatment of varices must be performed repeatedly until varices are eradicated and then followed by life long surveillance endoscopy to identify recurrent varices, a long term follow-up study would be important to determine the rebleeding and recurrence rates as well as the cumulative survival rates in alcoholic cirrhotic patients who have received injection sclerotherapy. Such a study would clarify the benefits of a long term surveillance programme and would define the incidence of endoscopic complications related to long term repeated sclerotherapy.

In order to answer this question, the first study reported in chapter 4 of this thesis evaluated the incidence of variceal eradication, variceal recurrence, rebleeding before variceal eradication and after variceal recurrence and death in a large cohort of patients with alcohol-induced cirrhosis and bleeding varices treated with repeated endoscopic variceal injection sclerotherapy. In addition, the study sought to determine the long term survival in alcoholic patients with cirrhosis who had bled from oesophageal varices and were treated with serial injection sclerotherapy. The study tested the validity of the hypothesis that eradication of oesophageal varices by repeated injection sclerotherapy would reduce recurrent variceal bleeding and death from bleeding varices.

The study evaluated 287 consecutive alcoholic cirrhotic patients who presented with acute oesophageal variceal bleeding and underwent a total of 2565 upper gastrointestinal endoscopic sessions which included 353 emergency and 1015 elective variceal injection treatments during the study period. In order to assess risk factors for rebleeding and death in a defined population and to minimize possible confounding variables, only those patients who had bleeding oesophageal varices due to alcohol related cirrhosis and who were treated with injection sclerotherapy were analysed. Patients with non-alcoholic cirrhosis or other causes of portal hypertension as well as those treated by endoscopic variceal ligation were excluded from the analysis. The diagnosis of cirrhosis was established by clinical evaluation, laboratory data, findings on radiological imaging including ultrasound and portal venous doppler assessment, and in selected patients, liver biopsy and hepatic vein wedge pressure measurements.

In all patients any variceal rebleeding episode that occurred after the index injection but before eradication was recorded as well as the percentage of patients in whom varices were eradicated. Patients whose varices recurred after eradication were documented and long term survival after eradication of varices was recorded. All oesophageal complications, including mucosal ulceration, perforation and strictures which occurred following the index sclerotherapy treatment or during subsequent endoscopic intervention were documented. The causes of death were recorded and cumulative overall survival in this study cohort was assessed at 1, 3 and 5 years by life table analysis.

## **Study 2**

There is consensus that endoscopic control of bleeding is the emergency treatment of choice if actively bleeding oesophageal varices are present during diagnostic endoscopy (D'Amico 2006, Burroughs 2008). However, data on the endoscopic control of major variceal bleeding and immediate mortality from uncontrolled bleeding in alcoholic cirrhotic patients is not sufficiently robust for an accurate or reliable estimate to be made from the existing literature. In 8 published studies which included 1488 patients, the median mortality in patients with uncontrolled bleeding within 48 hours of admission was 8% (D'Amico 1997). In addition to initial uncontrolled variceal bleeding, a substantial number of patients have early variceal rebleeding after successful initial endoscopic haemostasis. Early variceal rebleeding is associated with a significantly increased risk of death within 6 weeks, emphasizing that prevention of variceal rebleeding should be the primary objective of endoscopic intervention. The reported incidence of early rebleeding in the first 6 weeks after initial endoscopic control of bleeding ranges from 30% to 40% and the six week

mortality after the first variceal bleed varies from 30% to 50% in high risk patients (D'Amico 1997). No accurate or representative data exist for alcoholic cirrhotic patients with acute variceal bleeding.

The objective of the second study which is reported in chapter 5 of this thesis was to evaluate the efficacy of emergency endoscopic variceal injection sclerotherapy in achieving control of acute variceal bleeding and the frequency of acute variceal rebleeding and death within six weeks in a large cohort of alcoholic cirrhotic patients who presented to hospital with a first episode of acute variceal haemorrhage. In this study 310 alcoholic cirrhotic patients with acute variceal bleeding underwent 786 endoscopic variceal injection treatments of which 342 were emergency injections to control acute bleeding and 444 were subsequent elective injections during the first 6 weeks after the first variceal bleed. The study evaluated patients treated between January 1984 to December 2006. Most patients were Child-Pugh grades B and C. Endoscopic control of bleeding, variceal rebleeding, and survival were recorded in relation to Child-Pugh grades. Emergency endoscopic injection sclerotherapy, supplemented with balloon tamponade when necessary, controlled acute variceal bleeding in 304 of 310 (98%) patients. In 6 (1.9%) patients, variceal bleeding was not controlled despite using pharmacologic and endoscopic therapy and balloon tamponade. A further 32 patients had recurrent variceal bleeding within 5 days of initial endoscopic control and required further emergency endoscopic variceal injection procedures to achieve definitive endoscopic variceal haemostasis. The 5 day endoscopic failure rate in achieving variceal haemostasis was 12.3% (38 of 310 patients). Rebleeding after the initial 5 day assessment and up to 6 weeks after the index variceal injection occurred in 44 (15.7%) of the 281 patients who survived

more than 5 days. Of the 44 patients who rebled, 13 (29.5%) died in the 6 week period. Overall 75 (24.2%) patients rebled during the 6 week assessment period after initial control during the index admission. The incidence of rebleeding increased according to the Child-Pugh scores. Twenty five (15%) of the 166 patients who were Child-Pugh grade A and B rebled compared to 50 (34.7%) of the 153 patients in Child-Pugh grade C. Significantly more Child-Pugh grade C patients rebled than Child-Pugh grade A or B patients ( $p < 0.001$ ).

Seventy seven patients (24.8%) died during the 6 week study period. Twenty-nine (9.3%) died within 5 days of admission and 48 (15.4%) between day 6 and 42. No Child-Pugh grade A patients died, 14 Child-Pugh B patients died, and 63 Child-Pugh grade C patients died. Liver failure was the commonest cause of death and occurred in 29 patients. Twelve patients died of hepatorenal failure and 11 died of pneumonia and respiratory failure. Death in 25 patients was a consequence of continued or recurrent variceal bleeding. Survival at 5 days and 6 weeks in Child-Pugh grade A patients was 100% and 100%, in Child-Pugh grade B patients 96% and 92.7%, and in Child-Pugh grade C patients 83.4% and 73%, respectively. Significantly more Child-Pugh grade C patients died than Child-Pugh grade A or B patients. Mortality increased exponentially as the Child-Pugh score increased with a mortality of 78% for a Child-Pugh score of 14 and 83% for a Child-Pugh score of 15.

A total of 338 complications were documented in 159 patients during surveillance or unscheduled endoscopy after a prior variceal injection. Minor complications of sclerotherapy were common after acute injection for active bleeding and included dysphagia, transient fever and pulmonary atelectasis. Mucosal ulceration at an

injection site was found at follow-up endoscopy on 333 occasions in 155 patients. An oesophageal stricture at the injection site occurred in 5 patients after sclerotherapy. No strictures required oesophageal dilatation and all 5 resolved spontaneously.

### **Study 3**

Alcoholic liver disease is the leading cause of cirrhosis and portal hypertension in the developed world (Propst 1995). The natural history of alcoholic cirrhosis depends on the degree of liver decompensation, the presence of complications such as variceal bleeding, ascites or spontaneous bacterial peritonitis and the efficacy of the applied therapy. Progressive liver decompensation occurs more rapidly in patients with alcoholic cirrhosis than in those with cirrhosis due to viral hepatitis B or C and is aggravated by superadded alcoholic hepatitis. Once decompensation occurs in cirrhotic patients, mortality without organ replacement is as high as 85% over 5 years (Schuppan 2008). Defining prognosis is an essential part of the initial assessment of cirrhosis and constitutes the basis for treatment decisions. (D'Amico 2006). A number of patient features, characteristics and variables are related to and influence the course and outcome of cirrhosis and are relevant in formulating the prognosis. Several prognostic variables can be combined into a prognostic model to improve the prediction of outcome. While in theory the concept of prognostic modelling in cirrhotic patients may seem elementary, in practice the analysis is complex because there is a wide spectrum of clinical variations between patients. Patients may thus present at various stages of progression of cirrhosis and with different combinations of clinical features, different laboratory liver function values and different responses to the complications of cirrhosis and treatment (Christensen 1997). These variables

and differences among patients with cirrhosis make formulation of a prognostic model complex. To overcome the complexities of these variations, a large patient data base which includes the outcome variables and the intervention component for each patient is required. (Christensen 1997).

While several previous studies have attempted to develop a classification system that both characterises the degree of liver injury and predicts the prognosis of patients with cirrhosis on the basis of clinical and laboratory values, there currently is no consensus which specific risk factors have the best prognostic value for early rebleeding and mortality after variceal bleeding in alcoholic cirrhotic patients. The Child-Pugh classification is widely used because of its simplicity but because the classification was originally developed empirically, there are major flaws with poor discrimination between patients. The Child-Pugh scores may vary significantly between patients if single variables are modified or manipulated by medical treatment such as overzealous diuretic therapy, albumin infusion or ascitic paracentesis (Huo 2008). The original data in these scoring systems are variable and conflicting because of small sample sizes, referral bias, dissimilar study endpoints, differences in patient selection, aetiologies of cirrhosis, techniques of endoscopic intervention and the precise definition of rebleeding (de Franchis 2003).

Early rebleeding is the most consistently reported prognostic risk indicator of death at 6 weeks (Bureau 2008, Burroughs 2008, Krige 2009b). Accurate indicators predicting an increased risk of early rebleeding and early death could allow the selection of patients for more invasive treatment such as emergency transjugular

portosystemic shunting before their condition deteriorates precluding further therapy. Unfortunately the risk indicators identified to date are mainly indicators of poor liver or renal function which are also associated with a high operative risk and consequently are of limited clinical value (Triantos 2006).

The objective of the third study which is detailed in chapter 6 therefore was to identify by multivariate analysis in a large longitudinal cohort study a set of robust prognostic variables which could predict early rebleeding and death at 6 weeks in alcoholic cirrhotic patients admitted to hospital with a first variceal bleed and to confirm these risk factors by internal validation in a subsequent group of patients with bleeding oesophageal varices. As in the previous 2 studies outlined in chapters 4 and 5, the patient data in this study were recorded prospectively on a standard proforma and entered on a computer programme maintained by a dedicated research assistant. All patients received their first emergency and all subsequent endoscopic variceal sclerotherapy injections in our unit and only those patients who had bleeding oesophageal varices due to alcohol related cirrhosis and who were treated with injection sclerotherapy were analysed. Patients with non-alcoholic cirrhosis or other causes of portal hypertension as well as those treated by endoscopic variceal ligation were excluded from the analysis. The diagnosis of cirrhosis was confirmed by clinical evaluation, laboratory data, radiological imaging and, where necessary, by liver biopsy. The initial and the second sclerotherapy session, a week later, were performed during the index admission to hospital. Endoscopic details including the size of varices, the presence of active bleeding and the volume of sclerosant injected at each intervention were recorded. Subsequent sclerotherapy was undertaken at regular intervals at an outpatient clinic until the varices were eradicated.

In this study a retrospective analysis of the prospectively collected data in the 310 patients was performed to identify potential risk factors which could predict rebleeding and death. Fifteen variables related to clinical and biochemical data, as well as details of the endoscopic intervention including the size of varices and sclerosant volume, were analysed. The primary endpoints of the study were rebleeding and death at 42 days. *Time zero* was defined as the time of admission to our hospital. *Failure to control bleeding* was defined as continued bleeding despite endoscopic injection and the addition of pharmacotherapy and the use of balloon tamponade. *Rebleeding* was defined as any episode of upper gastrointestinal bleeding that occurred after the initial bleeding episode had been successfully controlled by sclerotherapy, or bleeding that occurred subsequently between scheduled treatment sessions. *Mortality* was defined as death from any cause. The study design and analysis was approved by the appropriately convened Departmental and Institutional Ethics and Research Committees of the Health Sciences Faculty of the University of Cape Town. Data-validation and quality-control procedures followed accepted international good clinical practice guidelines.

Continuous variables were dichotomized on the basis of existing literature. The tested variables included serum albumin level, international normalised ratio, total bilirubin level, ascites, encephalopathy, variceal size, sclerosant volume given per sclerotherapy session, the need for a blood transfusion and the volume of blood transfused during the bleeding episode. The categorical variables included gender, age, pitressin administration, the need for balloon tube tamponade and the number of variceal sclerotherapy injection sessions required to control the acute bleed.

In the statistical analysis, bivariate associations between categorical variables were analysed using the  $\chi^2$  test. The Kruskal-Wallis test was used to assess blood requirements in units of blood in each of the 3 Child-Pugh grades. Logistic regression was used to estimate the odds ratios with 95% confidence intervals for adjusted and unadjusted effects. Initially each risk factor was examined independently which produced the unadjusted odds ratios and 95% confidence intervals. The significant candidate variables identified by univariate analysis underwent multivariate logistic regression analysis to produce a prognostic model ("the training set") which represented the risk factors for rebleeding and death in the first 6 weeks after admission to hospital. The performance and discriminative ability of the constructed models to predict rebleeding and mortality at 6 weeks was assessed using receiver operating characteristic analysis. The prediction accuracy was quantified using the concordance index (C-index) which is equivalent to the area under the receiver operating characteristic curve and reflects the ability of a model to discriminate participants (or patients) who develop the event of interest (i.e. rebleeding or death) from those who do not. Values range from 0.5 to 1; a value of 1 is indicative of a model with perfect predictive power. For all analyses, a  $p$  value less than 0.05 and a 95% confidence interval that did not span unity were considered the thresholds of statistical significance. Stata software was used for statistical analysis. In the validation process the developed models were tested for validity and concordance in a further set of alcoholic cirrhotic patients with bleeding varices who were treated subsequently ("the test set"). Model discrimination between the training (derivation) set and the test (validation) set was evaluated using the C statistic.

In the literature review component of this thesis in chapter 2, peer review publications were evaluated to assess the historical perspective, natural history and pathogenesis of oesophageal variceal rupture. As knowledge of oesophageal venous anatomy is an essential prerequisite and the familiarity with the technique of endoscopic injection sclerotherapy of oesophageal varices is a fundamental requirement in the treatment of portal hypertensive bleeding, these topics were reviewed as well as the specific details of the technique of sclerotherapy, including intravariceal injection, paravariceal injection and combined intravariceal and paravariceal injection methods, the sclerosing agents used and the conventional endpoints of therapy.

In the comparative analysis section, the review assessed the efficacy of injection sclerotherapy in the treatment of acute bleeding oesophageal varices compared to surgical procedures including portocaval shunt and oesophageal transection. The review also evaluated the benefits and risks of injection sclerotherapy in the prevention of recurrent variceal bleeding compared to conservative treatment, beta-blockers, sclerotherapy plus beta-blockers, variceal band ligation, surgical shunts and transjugular intrahepatic portosystemic shunts. Finally, as injection sclerotherapy is an invasive endoscopic procedure which requires a high degree of manipulative skills, the spectrum of complications including oesophageal mucosal ulceration, rebleeding from patent residual varices, oesophageal perforation, intramural haematoma, oesophageal stricture and oesophageal motility disorders that may occur after injection of sclerosant were reviewed.

In the concluding chapter, the synopsis summarises the main findings and implications of the three clinical studies and recommendations for future directions of research in portal hypertension are suggested. Because the success of endoscopic therapy may be compromised by recurrent bleeding and serious procedure-related complications, recommendations regarding the technical aspects of sclerotherapy are included as well as the need to supervise trainees when critical decisions are required. Early and close multidisciplinary consultation is emphasized in demanding cases to facilitate appropriate therapy and optimal management. As the treatment of acute bleeding and prevention of recurrent variceal bleeding is best accomplished by a skilled, knowledgeable, and well equipped team using a multidisciplinary integrated approach, modern management requires the provision of the full spectrum of treatment options, including pharmacological therapy, endoscopic treatment, interventional radiological procedures, surgical shunts and liver transplantation

A review of the literature shows considerable variation in the quality of randomised trials in portal hypertension, and despite the plethora of studies, there remain deficiencies which leave unanswered questions. Understanding the problems inherent in the design, execution and interpretation of clinical trials in portal hypertension is critical in planning future studies. The statistical power of trials remains a major problem in portal hypertension studies. Improved appreciation of the principles involved in the design and implementation of clinical trials and analysis of data will increase the number of high quality of randomised controlled trials which should resolve some of the issues. There is a need to use standardised definitions for the critical end points in portal hypertension and bleeding varices and issues of

quality of life and cost effectiveness are becoming increasingly important concepts to include in trial design.

Future research into portal hypertension requires adequately powered, meticulously conducted, properly reported multicentre trials to address unresolved issues. As patient recruitment becomes an increasing impediment, future studies need internationally accepted and uniform protocols to facilitate aggregate analyses and future meta-analyses. In addition, the ever increasing demand for medical fiscal discipline and logistic efficiency require the issue of cost to be adequately addressed in prospective studies. Identification and knowledge of accurate prognostic predicting early rebleeding should ideally provide a powerful tool to identify at an early stage those patients in whom conventional treatment is likely to be unsuccessful and who require urgent implementation of an aggressive salvage strategy. Future prospective studies incorporating and evaluating the full spectrum of prognostic factors including clinical variables, liver biochemistry, endoscopy and portal pressures and comparative MELD and Child-Pugh assessment will be valuable advances in improving the effective and rational management of patients with bleeding oesophageal varices and portal hypertension.

## CHAPTER 2

### 2.1 HISTORICAL PERSPECTIVE OF SCLEROTHERAPY

The first report of the use of endoscopic injection of sclerosant into oesophageal varices to control variceal bleeding was published in 1939 by two Swedish surgeons, Clarence Crafoord and Paul Frenckner (Crafoord 1939). The patient was a 19-year old woman who had presented 2 years previously with bleeding oesophageal varices. She was noted to have an enlarged spleen with no clinical or biochemical evidence of liver disease and had an elective splenectomy. She remained well for two years when she had a further variceal bleed due to recurrent varices identified on rigid oesophagoscopy. Frenckner designed a special needle which could be advanced down a Jackson rigid oesophagoscope to inject the varices. During the initial intervention a total of 6ml of quinine was injected into three oesophageal varices without provoking further bleeding. When the oesophagoscopy was repeated five days later Crafoord and Frenckner found that the varices had reduced in size. A further series of injections was given every second day for one month until all the oesophageal varices had been eradicated. Follow-up oesophagoscopy at six month intervals confirmed that the varices had not recurred. The patient remained well without any further bleeding during the next three years when the case report was published (Crafoord 1939).

A second case report of injection sclerotherapy was published in 1940 by Herman Moersch, a thoracic surgeon at the Mayo Clinic in Rochester, Minnesota (Moersch 1940). Moersch treated a 30 year old man with cirrhosis who had first presented at the age of 18 years with variceal bleeding and had undergone a splenectomy. The

patient remained well with no further variceal bleeding for eight years. He then had several recurrent variceal bleeds and was admitted to hospital in 1940. Oesophagoscopy confirmed large oesophageal varices, one of which was injected with 0.5ml of a 2.5% solution of sodium morrhuate. The remaining varices were injected at four day intervals with 1ml of sodium morrhuate on each occasion. After these injections the varices were reduced in size and no further bleeding occurred in the three months up to the time of the report (Moersch 1940).

After these two case reports, injection sclerotherapy was introduced at the Mayo Clinic and at Baylor University Hospital in Dallas, Texas, to treat bleeding oesophageal varices. In June 1947 Herman Moersch from the Mayo Clinic and Cecil Patterson and Milford Rouse from Baylor University Hospital presented their experience at the American Gastroenterological Association Meeting in Atlantic City, New Jersey, and published their data in the same year in JAMA and Gastroenterology, reporting their long-term results of injection sclerotherapy (Moersch 1947, Patterson 1947). Moersch reported his experience in 22 patients who had received repeated injections as an elective procedure following variceal bleeding. Twelve of the 22 patients had no recurrence of bleeding after 3 years, 8 of whom had been followed for 4 years or more. Ten patients continued to bleed from varices, although only three died as a result. Moersch noted that most patients with recurrent variceal bleeding had gastric fundal varices which were not present in the twelve patients in whom therapy was successful. Moersch reported that two patients had died of recurrent variceal bleeding due to gastric varices which could not be controlled through the rigid oesophagoscope (Moersch 1947). The second presentation by Cecil Patterson and Milford Rouse from Baylor University Hospital

detailed the results of injection sclerotherapy in 24 patients who had a total of 76 sclerotherapy injection sessions using sodium morrhuate over a 4 year period. Six of the 24 patients died as a consequence of variceal bleeding, but the remaining 18 patients had only 8 bleeding episodes during follow-up (Patterson 1947).

Despite the initial enthusiasm and reported success, the introduction and increasing popularity of portocaval shunt operations which were described by Blakemore in 1946, overshadowed endoscopic injection sclerotherapy which was used infrequently during the next decade. The introduction of portal systemic shunt surgery in Great Britain and United States so dominated the management of portal hypertension and variceal bleeding that no further developments of injection sclerotherapy occurred for a decade (Westaby 1983). The next major series using injection sclerotherapy was published in 1955 in the British Medical Journal by Ronald Macbeth from Oxford who reported his experience in 30 patients, 14 of whom had cirrhosis and 16 who had portal or splenic vein thrombosis. Macbeth found the technique disappointing in patients with cirrhosis because of the high mortality in cirrhotic patients irrespective of the recurrence of variceal bleeding. However, in those with an extrahepatic cause of portal hypertension and normal liver function, the results were satisfactory and Macbeth recommended that this group was suitable for injection sclerotherapy (Macbeth 1955). Two other important points were made in this report. Firstly, there were no serious complications as a consequence of the injection sclerotherapy and, secondly, Macbeth stressed the need for further oesophagoscopy at six month intervals following initial obliteration to identify recurrent varices.

Fearon and Sass-Kortsak from Toronto reported their experience of injection sclerotherapy in children who had presented with variceal bleeding. Fifteen patients were treated over a 4 year period, ranging in age from 23 months to 16 years. Thirteen of the children had portal vein thrombosis and 2 had cirrhosis and received 1 to 8 injection sessions. Sclerotherapy was successful in 9 of the 15 patients with few or no further variceal bleeds following injection. In 6 patients variceal bleeding recurred despite repeated injections, and 2 patients died as a result of bleeding (Fearon 1959).

The early interventional endoscopists used rigid endoscopes and an intravariceal injection technique which was performed on an anaesthetised and intubated patient. Wodak, an Austrian surgeon, modified the technique of intravariceal injection sclerotherapy in 1960 by injecting not into the varix but in a paravariceal position into the submucosa alongside the varices with the aim of creating a fibrotic layer over the varices and to leave the underlying patent varices as functioning collaterals (Wodak 1960). This technique was adopted by others in Austria and Germany and, in particular, Denck and Paquet (Denck 1971, Paquet 1978).

In 1973 George Johnston and Harold Rodgers from the Royal Victoria Hospital in Belfast reported their experience of injection sclerotherapy over a 15 year period (Johnston 1973). Whereas Macbeth recommended repeated courses of injection to obliterate the varices, Johnston and Rodgers used only a single injection session to control the acute bleeding episode (Johnston 1973). Between 1958 and 1972, 177 patients who had a total of 194 bleeding episodes were treated by injection sclerotherapy. In 87 patients the cause of portal hypertension was cirrhosis,

whereas in 30 patients portal or splenic vein thrombosis was present. Bleeding was controlled in 177 of 194 episodes by sclerotherapy with a 93% success rate. Sixteen of 17 patients who continued to bleed, died as a result. Serious complications after sclerotherapy occurred in only 3 patients who developed full thickness oesophageal wall necrosis, one of whom died (Johnston 1973). In 1975 Bailey and Dawson described their modification of the rigid 50 cm Negus oesophagoscope in which a 0.5 x 4.0 cm slot was cut in the distal end diagonally opposite the beak as in a Gabriel proctoscope (Bailey 1975). This modification was a major technical advance and facilitated the injection of varices. The slot allowed a varix to prolapse into the lumen of the oesophagoscope which gave improved visibility, thus allowing accurate intravariceal injection of sclerosant.

However, by 1975, almost 40 years after the first use of injection sclerotherapy to control variceal bleeding, there were still no controlled data to confirm the efficacy of the technique and, in particular, whether survival was increased in the treated patients (Westaby 1983). To provide this important information Terblanche from Cape Town initiated the first controlled trial in August 1975. This study included patients with cirrhosis and portal or splenic vein thrombosis. Injections were given using the technique described by Bailey and Dawson, which Bailey had introduced to Cape Town during a visit in 1974. Repeated courses of injection were used to obliterate the varices. Although a control group was an integral part of this study, the trial design allowed patients in the control group to undergo a single course of sclerotherapy if they presented with variceal bleeding. The results of this trial were reported in 1979 when 24 patients were included in the analysis, 11 having received repeated injections and 13 in the control group (Terblanche 1979). Four of the 11

(36%) patients treated by injection had further episodes of variceal bleeding compared to 9 of 13 (69%) in the control group. Despite fewer bleeding episodes in those receiving repeated injections, survival for the two groups was similar. The failure to show a difference in survival may be explained by the policy of injecting those patients in the control group whenever bleeding occurred, which accounted for 18 separate injections in the 9 patients who had recurrent bleeding. A further analysis of this study showed a similar reduction in variceal bleeding in those undergoing repeated injection, but survival again was not improved (Terblanche 1983). In 1977 the Kings College group in London started a prospective randomised trial and reported their experience using sclerotherapy in 64 patients with a 57.7% one year survival. Of the 22 deaths in their series, 7 were due to uncontrolled variceal bleeding and 4 deaths were a result of oesophageal perforation related to the procedure (Clark 1980). Two subsequent papers were published with larger numbers (Macdougall 1982, Westaby 1985).

The next phase in the evolution of endoscopic control of variceal bleeding was the report from King's College Hospital by Williams and Dawson that a flexible fibre-optic endoscope passed through an outer sheath was able to provide effective control of variceal bleeding (Williams 1979). A prospective randomised trial from Cape Town which compared the rigid scope with flexible endoscopy showed that the flexible endoscope was as effective as the rigid scope in controlling acute variceal bleeding and variceal eradication and resulted in fewer complications such as oesophageal perforation and strictures (Bornman 1988). The results of the Cape Town trials, together with the Kings Hospital data and subsequent reports on the use of

sclerotherapy in the management of acute variceal bleeding led to a resurgence of interest in sclerotherapy in the early 1980s.

As the endoscopic technique evolved, experience showed that the overtube was not necessary during injection sclerotherapy, even for acute variceal sclerotherapy, and the use of the overtube became redundant. As flexible fibreoptic endoscopy became the standard of care, the rigid oesophagoscope became obsolete and patients had the procedure performed electively as an outpatient using conscious sedation. The next milestone in the evolution of endoscopic variceal treatment was the development of variceal banding by Stiegmann from Denver, Colorado, who had spent a sabbatical working with Terblanche and Bornman in Cape Town. The development and introduction of the first prototype used a single band delivery system which was passed through an over tube in the oesophagus (Stiegmann 1986). Subsequent progress led to a disposable multiband delivery system which could apply six bands sequentially without the need for reloading or the use of an overtube (Stiegmann 1992, Stiegmann 1996). Further advances in endoscope development have led to video endoscopy and narrow diameter endoscopes which are better tolerated by the patient.

## 2.2 VENOUS ANATOMY OF THE OESOPHAGUS

A clear understanding of variceal anatomy has played a key role in the development of endoscopic therapy. The adaptations and changes that occur in the venous anatomy of the oesophagus in patients with portal hypertension have significant clinical implications when endoscopic injection sclerotherapy, which deals directly with varices in the lower oesophagus, is used. Even under normal conditions, the lower end of the oesophagus is subject to constant physiological changes (Vianna 1987). Variations in venous pressure occur during respiration, which, when combined with lower oesophageal sphincter contraction and the interactions of the anatomic structures involved in preventing gastro-oesophageal reflux, generate complex mechanical effects in the lower oesophagus (Johnson 1966, Cohen 1972). The consequences of these mechanical changes are of particular relevance in relation to their influence on the low pressure venous drainage of the gastro-oesophageal junction which functions as a spontaneous communication between the portal and azygous venous systems (Kegaries 1934).

To fully appreciate the pathogenesis of acute variceal bleeding and the rationale for the efficacy and limitations of injection sclerotherapy, an understanding of the pathophysiology of portal hypertension and the changes that occur in the venous anatomy of patients with oesophageal varices is necessary. In the past, logistic difficulties and technical complexities prevented accurate studies of the venous anatomy of the lower oesophagus in patients with portal hypertension (Arakawa 1983). More recently, as technology has evolved and become increasingly sophisticated, a wide range of innovative investigations have produced images that

have provided a clearer understanding of the venous anatomy of the lower oesophagus in portal hypertension (Spence 1991, Spence 2000). These investigations have included the use of anatomical studies (Kitano 1986), corrosion casting, endoscopic ultrasound (Irisawa 2001) ultrasound microprobes (Obara 2006), multidetector computed tomographic techniques utilising three dimensional image software, Doppler ultrasound (McCormack 1983), percutaneous transhepatic portography and cineangiography, histology using image analysis (Spence 1984a, 1984b) and morphometry applying image analysis programmes (Vianna 1987).

The original studies used injections of silicone rubber, resin, and barium gelatin into cadaver and fresh post mortem specimens to demonstrate the angioarchitecture of the oesophagus (Arakawa 1985, Butler 1951, De Carvalho 1966, Kegaries 1934, Kitano 1986, Noda 1984, Vianna 1987). In a seminal study in 1934, Kegaries demonstrated that the oesophagus had four longitudinal venous draining trunks which had few cross anastomoses and a fine capillary anastomosis between the portal and systemic circulations (Kegaries 1934). The next major contribution was by Butler who described intrinsic veins consisting of a subepithelial and a submucosal plexus and peri-oesophageal extrinsic veins (Butler 1951). Subsequently McBeth confirmed Butler's findings and emphasised the importance of subepithelial veins in variceal bleeding. Beswick and Butler stressed the relevance of dilated subepithelial oesophageal veins above the cardia. De Carvalho published a detailed anatomic study of the lower oesophagus in 1966, also using injection techniques. He reported that the veins in the distal oesophagus were present mainly in the mucosa in the form of regular palisades extending 2 to 4 cm proximally from

the gastro-oesophageal junction, whereas in the stomach and proximal oesophagus the veins were mostly in the submucosa (De Carvalho 1966).

In an elegant and innovative study by Spence et al., the microvasculature of the lower oesophagus in normal and portal hypertensive patients was evaluated quantitatively using a computer assisted image analysis system which had been developed to assess both normal and diseased microvasculature (Spence 1984a, Spence 1984b). Twenty normal specimens of oesophagus and stomach and seven specimens from patients with varices were studied (Spence 1984b). The authors found that each specimen could be clearly subdivided into three zones. Zone 1 was the stomach where the mean relative area occupied by veins in the lamina propria was 2.6 per cent (s.e.m.  $\pm$  0.2) in the normal subjects and 3.7 per cent (s.e.m.  $\pm$  0.8) in the variceal specimens. Zone 2 began at the oesophagogastric junction and extended 2-5 cm into the lower oesophagus. The mean area occupied by veins in the lamina propria increased to 19.8 per cent (s.e.m.  $\pm$  1.2) in the normal and 32.8 per cent (s.e.m.  $\pm$  3.9) in the varices specimens. Zone 3 was the remainder of the proximal oesophagus and the mean area occupied by veins in the lamina propria was 4.9 per cent (s.e.m.  $\pm$  0.3) in the normal and 6.1 per cent (s.e.m.  $\pm$  0.5) in the varices specimens. Further analysis revealed that this increase in area occupied by veins in the distal oesophagus was due to an increase in both the number and size of vessels in the lamina propria of Zone 2. The authors concluded that these findings may explain the propensity for oesophageal varices to bleed mainly from the distal oesophagus.

Doppler ultrasound evaluation of the lower oesophagus through an endoscope has demonstrated a constant perforating vein extending from the perioesophageal plexus to the subepithelial and submucosal layers at 36 cm (McCormack 1983). Vianna et al. studied the normal anatomy of the distal oesophagus using a combination of radiographic techniques, corrosion casting, and morphometry (Vianna 1987). In their study four distinct zones of venous drainage were identified: (i) a gastric zone below the gastro-oesophageal junction which is characterised by longitudinal venous distribution; (ii) a palisade zone above the gastro-oesophageal junction which is composed of parallel veins within the lamina propria; (iii) a perforating zone in which veins traversed the wall of the oesophagus to connect the intrinsic and extrinsic systems and (iv) a truncal zone composed of four or five deep veins. These investigators suggested that this anatomic pattern implied that venous flow was bidirectional in the palisade zone and that this zone acted as a high-resistance watershed between the portal and azygos venous systems (Vianna 1987).

In a subsequent investigation the Cape Town group studied the lower oesophageal venous anatomy in post mortem specimens of patients who had had portal hypertension and oesophageal varices (Kitano 1986). A previously developed refined resin-casting technique was used which produced a three dimensional view of the angioarchitecture and a high level resolution of the oesophageal microvasculature (Kitano 1986). Four layers of veins were identified: (i) intraepithelial channels, (ii) a superficial venous plexus, (iii) deep intrinsic veins and (iv) adventitial veins. The study also confirmed the presence of perforating veins in the distal oesophagus. The superficial venous plexus communicated with the gastric venous plexus and the deep intrinsic veins form the varices in portal hypertension.

These varices were demonstrated to occur in three to five main trunks which had multiple communications with the superficial venous plexus. In the light of these anatomical findings, Kitano et al. postulated that a major episode of variceal bleeding occurs as a result of rupture of the large deep intrinsic variceal channels that lie adjacent to the epithelial surface, or from a major branch of the superficial venous plexus at a point near a direct connection to a large varix. Minor variceal bleeding, which stops spontaneously, may occur from a branch of the superficial venous plexus via a connection to a large varix or from smaller dilated intraepithelial channels (Kitano 1986).

These anatomical studies of the venous angioarchitecture of the lower oesophagus, added to the original influential work of the earlier investigators, have clarified the detailed anatomy of the critical zone of bleeding, and provided clues to the pathogenesis of variceal rupture (Spence 1983a, 1983b). The modern understanding of variceal anatomy is based on these studies and is detailed below.

The intrinsic veins of the oesophagus are divided into four well defined zones.

1. The gastric zone extends for 2 to 3 cm below the gastro-oesophageal junction and is the junctional or transition venous drainage zone between the stomach and lower oesophagus. The veins of the gastric zone are arranged radially, compared to the irregular venous network present in the rest of the stomach. The veins in the gastric zone lie in the submucosa and lamina propria and become confluent near the gastro-oesophageal junction and drain into the short gastric and left gastric veins (Vianna 1987)

2. The palisade zone is a continuation of the gastric zone and begins at the gastro-oesophageal junction and extends proximally for 2 to 3 cm. This zone corresponds to the abdominal oesophagus and anatomically is the segment of oesophagus between the gastro-oesophageal junction and the diaphragmatic hiatus. In this zone the veins are parallel and uniformly distributed and run longitudinally in palisades in four trunks which correspond to the oesophageal mucosal folds. Multiple anastomoses link these veins which occupy the lamina propria. There are no perforating veins in the palisade zone connecting the intrinsic and extrinsic veins of the distal oesophagus. Morphometric studies show that the cross sectional area of the veins at this level is increased compared to other levels. These observations support the notion that the palisade zone functions as a watershed between the portal and systemic circulations. This is the anatomic location of the lower oesophageal sphincter. When portal pressure rises and impedes venous drainage in the gastric zone into the left gastric vein, flow is directed via the veins in the palisade zone into the lower oesophagus and ultimately into the azygous system (Vianna 1987).

3. The perforating or transitional zone extends 2 to 3 cm up the oesophagus above the palisade zone and connects the palisade zone to the truncal zone. The main feature of this zone are the perforating veins which traverse the muscle wall of the oesophagus and link the internal and external oesophageal venous systems. This area is of significance in patients with portal hypertension because of variceal bleeding. Both endoscopic and histologic observations of the oesophagus show dilated veins in the lamina propria and the submucosa which are at risk for rupture. Noda confirmed the frequent occurrence of variceal bleeding in this zone, and labelled this as the "critical" area (Noda 1984). The intrinsic veins of the lower

oesophagus drain into the extrinsic veins primarily in the perforating zone via valved perforating veins that normally allow only unidirectional flow. These perforating veins occur circumferentially around the oesophageal wall. When flow is increased through these veins, as occurs in portal hypertension, the perforator valves become incompetent and allow bidirectional flow. The organized longitudinal venous structure in the oesophagus consequently is lost, as the veins become distended and form a network.

4. The truncal zone is 8 to 10 cm long and extends upwards in the oesophagus from the perforating zone. The truncal zone is characterized by four or five large longitudinal venous trunks in the submucosa. Blood in these veins flow in a cranial to caudal direction and drain via the perforating veins into the extrinsic veins of the oesophagus.

The modern understanding of the venous anatomy of the lower oesophagus explains the observation by previous investigators why varices tend to bleed 2 to 5cm above the gastro-oesophageal junction (Kitano 1986, Spence 1984b, Spence 1987). The constant perforating veins of the distal oesophagus and interconnections between layers of veins explain the re-appearance of varices after eradication (Terblanche 1983, McCormack 1983). The detailed anatomy of the critical zone of bleeding provides a clue to the pathogenesis of variceal rupture (Spence 1987). This information also provides an explanation for the early success of injection and for the frequent recurrence of varices after eradication by sclerotherapy (Spence 1987).

Haemodynamic studies of the portal system may provide valuable information on this point. It has been shown that an absence of extravariceal collateral channels, such as paraesophageal veins and spleno-gastro-renal veins, is an independent risk factor for elevation in portal pressure after sclerotherapy or ligation (Obara 2006). Thus, patients with poorly developed extravariceal collateral channels may be at risk for the recurrence. Although ligation is less invasive than sclerotherapy, the recurrence of oesophageal varices after ligation remains a significant problem. The recurrence rate of oesophageal varices is significantly higher in patients receiving ligation than in those with sclerotherapy (Hou 1995). This observation could be explained by the fact that ligation obliterates only mucosal and submucosal varices. In contrast, recent scientific evidence has shown that sclerotherapy obliterates deeper oesophageal veins, including perforating veins and para-oesophageal collaterals. Endoscopic Doppler ultrasonography has shown the presence of perforating veins as afferent veins in relation to oesophageal varices, suggesting that flow into the varices through perforators may be involved in oesophageal variceal dilatation and bleeding (Irisawa 2001). This hypothesis is further supported by recent endoscopic ultrasound evaluation in which the number and diameter of perforating veins positively correlates with the size of oesophageal varices. The recurrence of oesophageal varices after endoscopic therapy appears to depend on several factors, including as the presence of perforating veins, the endoscopic therapy technique used; the difference of anatomical features of para-oesophageal collaterals, and the development of the extravariceal collateral channels (Obara 2006). Further well-designed studies are needed to test this hypothesis.

## 2.3 THE NATURAL HISTORY OF VARICEAL BLEEDING

The modern management of the complications of portal hypertension is based on a sound understanding of the pathophysiology and the detailed knowledge of the development and natural history of oesophageal varices (Bosch 2003a). Portal hypertension results in the formation of an abundant collateral circulation connecting portal blood vessels with the general circulation. The adaptative capacity of the portal circulation is individual-specific and depends mainly on the size of intra- and extrahepatic collateral vascular communication between portal and systemic circulations (Cichoz-Lach 2008). From the clinical and haemodynamic perspective, the most important collaterals form in the gastro-oesophageal area which results in oesophageal varices in 80 to 90% of patients.

Recent research has influenced knowledge on the pathophysiology of portal hypertension (Cichoz-Lach 2008). The observation that the formation of collateral veins in response to portal hypertension does not result in decompression of the portal venous system and fails to decrease portal pressure suggests that other mechanisms besides anatomical mechanical resistance are involved in the development and persistence of portal hypertension (Tsai 2007, Cichoz-Lach 2008).

The application of physics dictates that blood pressure in a vascular system is defined by the formula:  $\text{pressure} = \text{vascular resistance} \times \text{blood flow}$  (Cichoz-Lach 2008). In the portal hypertension model the increase in pressure is a result of increased vascular resistance and an increased blood volume in the portal vascular bed. A further significant factor influencing portal pressure is increased blood flow in the portal circulation due to a hyperkinetic circulation which manifests as increased

cardiac output and generalized vasodilation of the vascular bed (Tsai 2007). Increased portal flow in turn increases further changes within blood vessels thus enhancing vascular resistance.

Portal hypertension is associated with changes in the intrahepatic, systemic, and portosystemic collateral circulation. Alterations in vasoreactivity (vasodilation and vasoconstriction) play a central role in the pathogenesis of portal hypertension by contributing to increased intrahepatic resistance, hyperdynamic circulation, and expansion of the collateral circulation. Portal hypertension is also characterised by changes in vascular structure termed vascular remodeling, which is an adaptive response of the vessel wall that occurs in response to chronic changes in the environment such as shear stress. These complementary processes of vasoreactivity and vascular remodelling contribute to increased intrahepatic resistance and represent important targets in the treatment of portal hypertension (Shah 2007).

Subsequent research has identified additional factors that influence portal blood flow and result in increased portal pressure. Vitamin A-rich hepatic stellate cells constitute 15% of all hepatic cells and once activated, play the role of myofibroblasts which are the main source of collagen, fibronectin and other components of extracellular matrix (Mallat 1998, Reeves 2002). Hepatic stellate cells, also called Ito cells, are found in perisinusoidal spaces of the liver and significantly modulate blood flow through the hepatic sinuses. Their activity is regulated by endothelial factors: endothelin (the activation of its receptor constricts muscular cells in the portal vascular bed wall) and NO (Chen 2008, Rockey 2006, Reynaert 2002).

The initial factor in the pathophysiology of portal hypertension is an increase in vascular resistance to portal blood flow (Bosch 2003b). In alcohol-induced cirrhosis this increase in resistance occurs at the hepatic microcirculation level and produces sinusoidal portal hypertension. The increase in hepatic vascular resistance in cirrhosis is a consequence of the mechanical distortion of the hepatic architecture caused by nodular regeneration and bridging fibrosis and also by a dynamic component due to active contraction of portal and septal myofibroblasts, activated stellate cells and portal venules (Rockey 1996, Pinzani 1999, Wiest 2002). This increase in intrahepatic vascular tone is modulated by increased activity of endogenous vasoconstrictors including endothelin, alpha-adrenergic stimulus, leukotrienes, thromboxane A and angiotension II, and is lessened by nitric oxide, prostacyclin and vasodilating drugs such as organic nitrates, adrenergic agents, and calcium channel blockers (Bosch 2003b). A second and major contributing factor to portal hypertension is an increase in blood flow through the portal venous system, due to splanchnic arteriolar vasodilatation, which is caused by an excessive release of endogenous endothelial, neural and humoral vasodilators (Cichoz-Lach 2008).

Biologically active vasodilators including nitric oxide (NO), glucagon, prostaglandins, bile acids, TNF- $\alpha$ , and carbon monoxide increase portal flow and play an important role. An imbalance between the hyperresponsiveness and overproduction of vasoconstrictors (mainly endothelin-1 and cyclooxygenase-derived prostaglandins) and the hyporesponsiveness and impaired production of vasodilators (mainly NO) are the mechanisms responsible of the increased vascular tone in the sinusoidal/postsinusoidal area. Recent investigations have found different availabilities of NO in the intrahepatic circulation with preserved production in the

presinusoidal area and impaired production in the sinusoidal/postsinusoidal area. Decreased vascular resistance in the presinusoidal area of the liver is caused by increased concentrations of NO and adenosine. In case of portal hypertension however NO is not produced in the presinusoidal system and its production is disturbed or substantially decreased in the sinusoidal/postsinusoidal area (Watanabe 2007, Zipprich 2007). Thus altered vascular vasoreactivity is considered an important pathogenetic factor of portal hypertension which produces vasoconstriction or vasodilation which causes increased vascular resistance, hyperkinetic circulation and formation of collateral portal circulation (Shah 2007)

The principal factor influencing the clinical significance of portal hypertension and determining the development of complications is an increase in portal pressure above a critical threshold value. The threshold pressure for the development of varices in alcoholic cirrhosis is 12 mmHg (Garcia-Tsao 2008) while variceal bleeding occurs at a threshold pressure of approximately 22 mmHg (Cichoż-Lach 2008).

## 2.4 THE PATHOGENESIS OF VARICEAL BLEEDING

The pathogenesis of variceal rupture is related to the consequence of several physical factors within the wall of the varix. Portal pressure, variceal size, and epithelial thickness contribute to the likelihood of variceal rupture as related by the law of Laplace. According to Frank's modification of Laplace's Law, variceal wall tension is directly proportional to the transmural variceal pressure (the gradient between intravariceal and oesophageal luminal pressures) and the radius of the varix, and inversely proportional to the thickness of the variceal wall (Bosch 2003b). While variceal size is a function of variceal radius, red weal marks may represent areas of reduced wall thickness. Hepatic venous pressure gradient (HVPG) may constitute a good surrogate marker of transmural variceal pressure (Escorsell 2000, Bosch 2003a, Cichoż-Lach 2008). Cross-sectional and longitudinal studies demonstrate that variceal bleeding does not occur if HVPG remains below 12 mmHg (Feu 1995, Vorobioff 1996, Escorsell 2000). The risk of bleeding is independently associated with variceal size. Physical appearance also predicts bleeding, including the endoscopic variceal stigmata including, cherry red spots, haemocystic spots and diffuse erythema.

When cirrhosis is first diagnosed, varices are present in 40% of patients with compensated cirrhosis and in 60% of patients with ascites. (de Franchis 2007). After the initial diagnosis of cirrhosis, about 5% of patients develop new varices per year. (D'Amico 2006). Once developed, varices increase in size from small to large at a rate of 10-15% per year (Garcia-Pagan 2008). Progression of liver failure has the greatest influence on the increase in size of varices (Dell'Era 2008) while an

improvement in liver function and abstinence from alcohol may result in decrease in size of varices (Villanueva 2008a).

Once varices are present, the incidence of variceal bleeding is about 25% at 2 years in non-selected patients (de Franchis 2007). The most important predictive factors related to the risk of variceal bleeding are variceal size, presence of variceal endoscopic stigmata, and the severity of liver dysfunction as expressed by components of the Child-Pugh classification (Villanueva 2008b). Variceal size is the best predictor of variceal bleeding, and this is the variable used to decide whether a patient should receive prophylactic beta blockers or not (Sharara 2001). The risk of variceal bleeding is approximately 7% at 2 years in patients with small varices (<5 mm), and increases to 30% at 2 years in patients with large varices (de Franchis 2007). Variceal size and red colour signs are associated with an increased risk of bleeding because both contribute to an increase in the tension of the wall of the varices, the decisive factor determining variceal rupture (Bosch 2003a).

It has been reported that 30% of cirrhotic patients with an acute variceal bleeding episode die within 6 weeks (Bosch 2003b), but it is likely that this figure overestimates the current mortality from variceal bleeding (Garcia-Tsao 2008). A more accurate current figure would be a mortality of 20% at 6 weeks (de Franchis 2007). Immediate mortality from uncontrolled bleeding is in the range of 5-8% (D'Amico 2006).

Active bleeding at endoscopy (Ben Ari 1999), bacterial infection (Goulis 1998) and HVPG >20 mmHg measured early after admission (Moitinho 1999) are significant

prognostic indicators of failure to control bleeding. It is important to emphasize that variceal bleeding stops spontaneously in 40-50% of patients (de Franchis 2007). This is probably influenced by the fact that hypovolemia leads to reflex splanchnic vasoconstriction with reduced portal pressure and blood flow, a beneficial response that is nullified by blood transfusion (Kravetz 2007). The incidence of early rebleeding ranges between 30 and 40% within the first 6 weeks. (Kriger 2009a). The risk peaks in the first 5 days with 40% of all rebleeding episodes occurring in this early period (de Franchis 2007). Bleeding gastric varices, active bleeding at emergency endoscopy, low serum albumin levels, renal failure and HVPG > 20 mmHg have been reported as significant indicators of early rebleeding risk (Thomopoulos 2006). Early rebleeding (Ben Ari 1999) and renal failure (Cardenas 2001) are important prognostic factors for 6-week mortality, suggesting that their prevention should be a primary objective in the therapeutic approach to variceal bleeding.

Patients surviving a first episode of variceal bleeding have a high risk of rebleeding and death. The median rebleeding incidence within 1-2 years in untreated controls of randomised controlled trials of non-surgical treatment for prevention of recurrent bleeding reported after 1981 is 63% and the corresponding mortality figure is 33% (D'Amico 2006). Because of these high risks, all patients surviving a variceal bleeding should be treated for prevention of rebleeding independent of other risk indicators). Risk accepted indicators of rebleeding and death are variceal size, Child-Pugh grade, continued alcohol abuse and hepatocellular carcinoma (Villanueva 2008a).

## 2.5 INJECTION SCLEROTHERAPY OF OESOPHAGEAL VARICES

### Technique of injection

- 2.5.1 Intravariceal injection
- 2.5.2 Paravariceal injection
- 2.5.3 Combined intravariceal and paravariceal injection
- 2.5.4 Sclerosing agents
- 2.5.5 Endpoints of therapy

Variceal bleeding usually occurs from the lower 5cm of the oesophagus (Park 2008). Endoscopic injection sclerotherapy (EIS) of oesophageal varices is designed to control acute variceal bleeding and prevent subsequent bleeding by thrombosing the varices or thickening the mucosa overlying the varices (Krige 2005). Unlike the operations used in the treatment of portal hypertension which are specific and standardised, sclerotherapy is performed with different protocols using variable frequencies of injections and endoscopic review. A considerable number of variables influence the success of endoscopic intervention of bleeding oesophageal varices. Several variables are patient dependent and include the cause of portal hypertension, underlying hepatic reserve, hepatic haemodynamics, variceal size and the magnitude and effects of variceal bleeding on liver decompensation. In addition, several technical variables may affect the outcome of any individual sclerotherapy session or clinical trial (Krige 1999). These variables include the type and concentration of the sclerosant solution, the injection site, injection volume and frequency of injections. Despite the widespread popularity of the procedure for control of acute variceal bleeding, sclerotherapy technique remains, to a great extent, empiric and individualized (Krige 2000b). Several basic issues of methodology remain largely unanswered (Krige 2009a). It is not surprising therefore

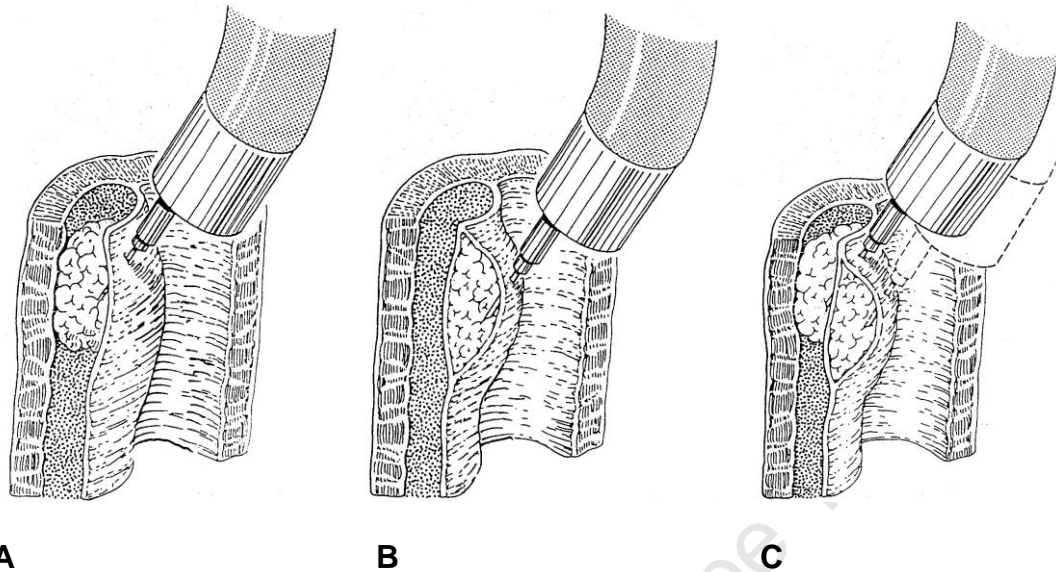
that controlled trials comparing sclerotherapy with other specific therapies, including variceal ligation, have yielded conflicting results (Krige 2005).

A variety of sclerosants with different mechanisms of action and varying complication rates have been used (Krige 2000b, Krige 2005). Tetradecyl sodium (1-3% solution), sodium morrhuate (5% solution) and ethanolamine oleate (5% solution) have been the most commonly used sclerosant agents in the USA (Krige 2007b). Outside North America, 5% ethanolamine oleate and 1% polidocanol have been used; polidocanol has been used predominantly for paravariceal injections (Park 2008). The ideal sclerosant and the best route of administration have yet to be defined, although the few controlled trials available favour ethanolamine oleate for intravariceal and combined therapy. In addition to sclerosants, two types of tissue adhesives, *histoacryl* and *bucrylate* have been used to treat variceal bleeding (Krige 2005). These tissue adhesives have proved effective in the control of variceal bleeding with a 90% success rate (Park 2008).

### **Injection sclerotherapy techniques**

Three different endoscopic techniques are used for injection sclerotherapy (Figure 2.5.1). Bleeding from oesophageal varices may be controlled by injecting the sclerosant directly into the variceal channel (i.e. intravariceal method), into the submucosa adjacent to or overlying the variceal column (i.e. paravariceal method), or a combination of both. Intravariceal injection is favoured by most endoscopists in the United States. Usually 1 to 5 ml of sclerosant, depending on the size of the varix, is injected directly into the variceal lumen immediately above the gastroesophageal junction, with an additional injection into the same variceal column more proximally, if

the varix is large. The goal of this technique is thrombosis of the varix and eventual obliteration of all channels in the distal 5 cm of the oesophagus.



**Figure 2.5.1** Technical variants of injection sclerotherapy. **A:** Intravariceal injection  
**B:** Paravariceal or submucosal injection. **C:** Combined intravariceal and paravariceal injections (Krige 2007a)

The paravariceal technique, which has been widely used in Europe, is performed by placing multiple injections using 0.5 to 1.5 ml of 0.5% or 1% polidocanol at each site beside the varices, commencing at the oesophagogastric junction, and proceeding upwards in a helical fashion, raising a wheal at each injection site. The theory is that paravariceal injection produces oedema of the submucosa to stop acute variceal bleeding and provokes fibrogenesis which subsequently causes thickening of the submucosa with a protective fibrous cover to sheath the varices and prevent bleeding while preserving the underlying varices as collateral channels. Both techniques appear satisfactory for treatment of variceal haemorrhage. Many

endoscopy departments, including the unit in Cape Town, use a combination of these two techniques (Krige 2007a).

Most endoscopists perform sclerotherapy as described above using no special equipment other than the endoscope and injector needle ('freehand technique'). A variety of ancillary devices including flexible endoscopic overtubes and balloons have been used in the past to improve the visibility and accuracy of sclerosant injection. In general, such devices have not produced results superior to freehand injection for control of acute bleeding, nor has the routine use of postsclerotherapy balloon tamponade been shown to improve outcome for treatment of active bleeding. With few exceptions, sclerotherapy is performed using a fibre-optic endoscope and a freehand technique without an oversheath.

The Cape Town endoscopy unit protocol advises a combined para- and intravariceal technique for the management of acute variceal bleeding and utilizes a predominantly intravariceal technique for long-term management when varices are small (Krige 2007a). The Cape Town endoscopy unit sclerosant of choice is 5% ethanolamine oleate. In most endoscopy units, injection treatments are continued at weekly intervals until the varices have been eradicated. Thereafter, the patient is assessed with surveillance endoscopy at 3 months and then at 6-monthly intervals. Whenever recurrent varices are found, a repeat course of weekly sclerotherapy is undertaken until re-eradication is achieved (Krige 2006b).

Trained assistants are essential and adequate resuscitative facilities must be available for all procedures. A flexible endoscope is used without general

anesthesia. Either an end-viewing or side-viewing instrument can be used. The end-viewing instrument is more versatile for both diagnosis and therapy, although the oblique-viewing instrument has the advantage of better visualization of the greater and lesser curves of the stomach, while the built-in forceps elevator helps to aim the injector, particularly for small varices during elective sclerotherapy. Several disposable sclerotherapy injectors with retractable needles within a Teflon coated plastic sheath are commercially available and are preferable to the flexible, reusable, metal injectors. Injectors have either a 23- or 25-gauge needle attached. The larger needle is preferred because this facilitates injection of the viscous sclerosant solution (Krige 1994).

Stuporous or comatose patients must have the airway protected by prior endotracheal intubation. If the patient has a balloon tube in situ, the balloons are deflated and the tube removed only when the endoscopy staff is ready to begin endoscopy and variceal sclerotherapy or ligation. Once the bleeding varix has been controlled, the remaining varices are injected or banded and the diagnostic endoscopy completed.

### **Elective sclerotherapy technique**

Elective sclerotherapy is performed in the endoscopy clinic where two assistants who are trained in endoscopy techniques are available. One assistant reassures the patient, provides suction of the patient's mouth to avoid aspiration, and ensures that the bite guard is not dislodged. The other nurse assistant advances and retracts the injector needle and administers the sclerosant under the direction of the endoscopist. The patient is placed in the left lateral decubitus position on the endoscopy bed with

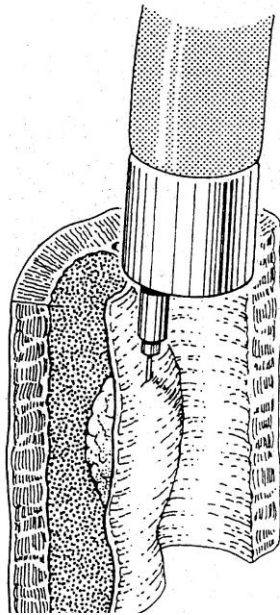
the head on a pillow and the neck slightly flexed. The pharynx and posterior tongue are anesthetized with 10% Xylocaine topical spray. A small butterfly needle is inserted into a superficial hand vein for administration of sedation. The Cape Town unit uses small incremental doses of midazolam up to 5 mg. All the instruments including the endoscope are checked prior to use, and commands such as 'advance needle' and 'retract needle' are rehearsed if an inexperienced assistant is present. Each time an injection is required, this is called for by the endoscopist and acknowledged by the assistant. The assistant is instructed to comment if resistance is encountered during injection because this may indicate that the varix is thrombosed or that the needle is not correctly positioned (Krige 1994, Krige 2007).

The endoscope is inserted through the mouthguard and passed through the cricopharynx into the oesophagus. Small amounts of air are insufflated intermittently to maintain sufficient distention of the lumen for adequate visibility. Mucus and fluid are removed through the suction channel and the lens cleared with a water jet when necessary. The entire oesophagus is examined and the presence of oesophageal varices noted. The number, size and extent of varices and the presence of endoscopic variceal stigmata (cherry red spots and red wheal marks) are documented. During elective endoscopy, the varices are usually not bleeding and a full diagnostic panendoscopy is performed to exclude other lesions before injecting the varices. The presence and extent of gastric varices and portal hypertensive gastropathy are noted and documented (Krige 2007a).

On completion of the panendoscopy, the endoscope is partially withdrawn into the lower oesophagus and positioned above the oesophagogastric junction so that the

varices in the lower 5 cm of the oesophagus can be injected. The endoscope tip is manoeuvred into position and the target varix identified. The endoscopist then passes the injecting catheter through the biopsy channel into the field of view and the tip of the catheter is positioned 2 cm beyond the end of the endoscope. To prevent the needle damaging the injector sheath or the endoscope channel, the injecting catheter is only passed when the endoscope tip is in a non-flexed position. The needle should remain in the retracted position until the tip of the injecting catheter has passed through the endoscope and is visible to the endoscopist. All movements and manipulations of the injector are performed only by the endoscopist. A practice aiming pass of the catheter, with the needle retracted within the sheath before the first injection, is useful to determine the precise direction of the advancing needle in relation to the target varix. The assistant advances the needle on instruction, and a small volume of sclerosant solution is discarded into the lumen of the oesophagus to ensure that the injecting catheter is filled with sclerosant and that residual air has been expelled. The endoscopist inserts the needle directly into the centre of the most prominent part of the varix, near to the oesophagogastric junction, by advancing the injector a further 5 mm. Once the needle has been satisfactorily placed within the lumen of the varix, the assistant is instructed to inject 1ml of sclerosant (Fig. 5.2.2). If this is achieved without resistance, further sclerosant is placed within the lumen of the varix, the assistant is instructed to inject 1 ml of injected under instruction. The varix should be seen to blanch and distend above and below the injection site. A total volume of no more than 5 ml of ethanolamine oleate is usually sufficient for a large varix. Smaller varices require less sclerosant. Thereafter, any additional varices are injected at the same level. A second injection

is placed 2–3 cm higher in large varices. Usually, only 2–3 ml of sclerosant is injected into the upper site (Krige 1994, Krige 2007a).



**Figure 2.5.2** Intravariceal injection technique (Krige 2007a).

Accurate positioning and placement of the needle is critical to achieve effective and accurate delivery of sclerosant and to avoid complications which may follow incorrect injection. A flat angle for needle insertion is preferable and avoids a deep injection: a perpendicular approach may transfix the varix and penetrate the underlying esophageal wall, resulting in an intramural injection of sclerosant. In this situation increased resistance to injection will be noted by the assistant and no blanching or distention of the varix will occur. The needle should be withdrawn and a further injection performed after accurate placement of the needle. Only the needle should enter the varix. Care must be taken to ensure that neither the needle hub nor the injecting sheath are inadvertently pushed through the variceal wall as this will leave a large defect which may give rise to troublesome bleeding. No attempt should be

made to inject the varices while the patient is restless or heaving. Uncontrolled injections may result in laceration of the varix by the needle with resultant major bleeding (Krige 2007a). After the procedure, the patient is observed in the endoscopy suite recovery room until fully awake and then discharged home in the care of a family member or friend. It is unusual for bleeding to complicate an elective sclerotherapy session. Subsequent sclerotherapy injections are performed at weekly intervals until all the varices have been eradicated. Severe local oesophageal mucosal ulceration may delay injection of a specific underlying varix, but the other variceal channels can be injected. Once varices have been eradicated, a further endoscopic assessment is performed at 3 months to confirm eradication. Further evaluations are performed 6-monthly or annually for life. If recurrent varices are noted during surveillance endoscopy, these are injected and repeat endoscopy and injections are performed at weekly intervals until the varices have been re-eradicated (Krige 2000b).

### **Emergency sclerotherapy technique**

The emergency resuscitative measures required are presented in chapter 3. The patient should be as stable as possible before commencing sclerotherapy. The procedure is performed in a specially equipped endoscopy suite. If the patient is obtunded or severely encephalopathic, an endotracheal tube will have been inserted. Severely ill patients should have the injection treatment performed in the intensive care unit. When major bleeding has occurred, the endoscopy is performed in the operating room where full resuscitative facilities, appropriate monitoring, intubation equipment and experienced anesthetic assistance is available.

The patient is placed in the left lateral decubitus position, as for elective sclerotherapy. However, if active bleeding is present and visibility is obscured, the table head is elevated to 30° to improve visualization. The lower oesophagus is flushed with saline through the irrigation channel and residual blood and fluid aspirated through the suction channel. Further insufflation usually provides adequate visualization to perform the first injection.

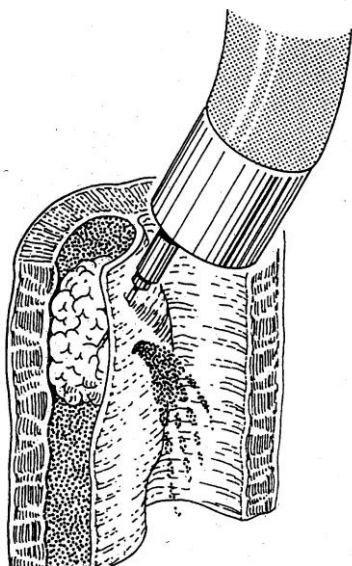
### **Intravariceal Injection**

Active variceal bleeding is immediately dealt with by controlling the bleed with intravariceal sclerotherapy. Urgent control of bleeding with accurate placement of the needle and sclerosant injection should be performed without delay while there is adequate visibility. No attempt should be made to insert the needle into the bleeding point, because this may enlarge the hole and aggravate bleeding with extravasation and loss of sclerosant. A technique similar to elective intravariceal sclerotherapy is used with needle insertion immediately proximal to the bleeding site (Fig. 5.2.3). A total volume of 5 ml of sclerosant is usually sufficient. Distention and blanching of the varix indicate that the needle is in the correct position and that the appropriate volume of sclerosant has been injected. After the bleeding has been controlled, the remaining variceal channels are sclerosed. A second series of injections is usually performed at a higher level. Panendoscopy is undertaken on completion of sclerotherapy to exclude other mucosal lesions (Krige 1996).

### **Combined paravariceal and intravariceal injection technique**

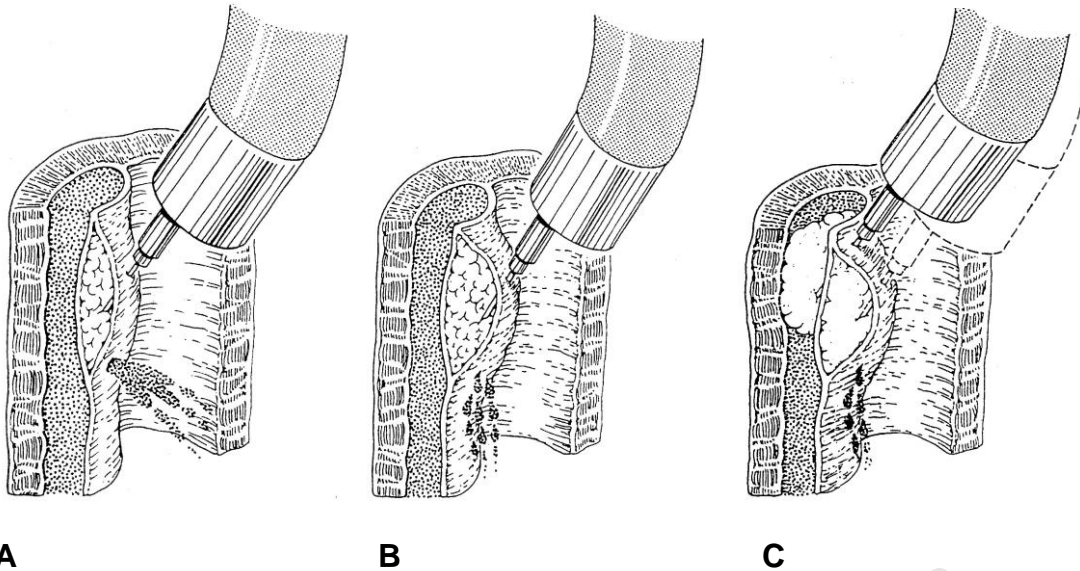
The Cape Town endoscopy unit recommends this technique to control active variceal bleeding. The needle is inserted into the submucosa in a paravariceal

position and 5% ethanolamine oleate injected proximal to the bleeding point to



**Figure 2.5.3** Emergency sclerotherapy: intravariceal injection technique (Krige 2007a).

compress the bleeding site by raising a wheal (Fig. 5.2.4). Sufficient sclerosant is injected to control the bleeding. If this does not completely control the acute bleeding, the paravariceal injection is repeated alongside the bleeding point. The procedure is completed by injecting the varix intravariceally (Fig.5.2.4). The volume injected paravariceally should not exceed 1 ml at each site to avoid ulceration of mucosa. The remaining variceal channels are then sclerosed. If variceal bleeding is profuse, vigorous lavage through the endoscope channel and elevation of the head of the table to 30° usually improves visibility and allows identification of the bleeding site. No blind attempts at injection should be used. If immediate sclerotherapy cannot be performed because of lack of expertise or inadequate visibility, bleeding should first be controlled by balloon tube tamponade before the patient has further sclerotherapy (Krige 1996, Krige 2007b).



**Figure 2.5.4** Emergency sclerotherapy: combined paravariceal and intravariceal injection technique. **A:** The initial paravariceal injection proximal to the bleeding point. **B:** Bleeding is controlled by the paravariceal submucosal injection. **C:** An intravariceal injections completes the procedure (Krige 2007a).

Most patients (70%) respond to a single injection treatment and have no further bleeds. If bleeding does recur, intravenous octreotide or somatostatin is recommended and the patient is re-endoscoped. Further bleeding varices are treated as before. If bleeding results from an injection site oesophageal ulcer, the intravenous octreotide or somatostatin infusion is continued and oral sucralfate administered. The success rate of a single injection treatment is 70%. Some 30% of patients will have a further bleed and require an additional injection treatment. Two injection treatments usually control variceal bleeding in over 95% of patients. Subsequently, repeated sclerotherapy sessions are undertaken at weekly intervals until all varices have been eradicated.

If further bleeding occurs after two injection treatments during a single hospital admission, this is defined as failure of emergency endoscopic therapy and the patient should have a Sengstaken balloon tube inserted. After resuscitation the patient is assessed and has an alternative procedure, usually a TIPS shunt.

University of Cape Town

## 2.6 COMPARATIVE STUDIES IN ACUTE VARICEAL BLEEDING

### 2.6.1. Sclerotherapy compared to vasoconstrictors in acute bleeding varices

Two major classes of vasoactive drugs, vasopressin and somatostatin, have been used to treat acute variceal bleeding. These drugs exert their effects either by reducing inflow of portal blood or by diminishing intrahepatic or collateral resistance. Varices are unlikely to bleed when portal venous pressure is below 12 mm Hg. Vasopressin is a potent but non-selective vasoconstrictor. Its use, however, is hampered by frequent and serious systemic vasoconstrictive side effects, especially in patients who have cardiac ischaemia and peripheral vascular disease. Consequently the role of vasopressin has declined appreciably since the introduction of newer and safer drugs. Terlipressin (triglycyl lysine vasopressin), a vasopressin analogue which has replaced the original vasopressin, undergoes cleavage of the glycyl residue after administration to allow the slow release of lysine vasopressin which does not have the deleterious cardiac side effects of vasopressin (Villanueva 2008). Somatostatin and its long-acting analogues, octreotide and vapreotide, are increasingly being used in the management of active variceal bleeding because both have selective vasoconstrictive effects on the splanchnic circulation and inhibit the production of the vasodilator, glucagon (Dell'Era 2008).

The efficacy of emergency endoscopic injection sclerotherapy in patients with acutely bleeding oesophageal varices has been compared with vasoactive drugs in 15 randomised controlled trials and assessed in a Cochrane meta-analysis (D'Amico 2003) The authors performed a meta-analysis comparing emergency sclerotherapy with pharmacologic treatment by searching Medline (1968-2002), Embase (1986-

2002), and the Cochrane Library (2002) to retrieve randomised controlled trials comparing sclerotherapy with vasopressin (+/-nitroglycerin), terlipressin, somatostatin, or octreotide for variceal bleeding in cirrhosis. Two independent reviewers identified eligible trials and extracted data. Outcome measures were failure to control bleeding, five-day treatment failure, rebleeding before other elective treatments, 42-day rebleeding, mortality before other elective treatments, 42-day mortality, number of blood transfusions, and adverse events. Data were analysed by a random effects model according to the vasoactive treatment. Sensitivity analyses included combined analysis of all the trials irrespective of the vasoactive drug, fixed effects model analyses, type of publication, methodological quality, and adequacy of generation of the randomisation list and of allocation concealment.

Fifteen trials were identified. Sclerotherapy was not superior to terlipressin, somatostatin, or octreotide for any outcome and to vasopressin for rebleeding, blood transfusions, death, and adverse events; it was superior to vasopressin for the control of bleeding in a single trial flawed by a potential detection bias. Sclerotherapy was associated with significantly more adverse events than somatostatin. In a predefined sensitivity analysis, combining all of the trials irrespective of the control treatment, risk differences (sclerotherapy minus control) and confidence intervals (CIs) were as follows: failure to control bleeding, -0.03 (-0.06 to 0.01); mortality, -0.035 (-0.07 to 0.008); adverse events, 0.08 (0.02 to 0.14). Mortality risk difference was -0.01 (-0.07 to 0.04) in good-quality trials and -0.08 (-0.14 to -0.02) in poor-quality trials. The authors concluded that available evidence did not support emergency sclerotherapy as a single first-line treatment of variceal bleeding in cirrhosis when compared with vasoactive drugs, which control bleeding in

83% of patients and suggested that endoscopic therapy might be added in pharmacologic treatment failures.

A further meta-analysis from the group at the Royal Free Hospital, London, had a different conclusion (Triantos 2006). Their meta-analysis was performed to evaluate whether sclerotherapy remains a gold standard in acute variceal bleeding. Sclerotherapy was evaluated across four randomised trial groups: (a) combined with vasoconstrictors compared to vasoconstrictors alone (five trials with 400 patients); (b) compared to vasoconstrictors alone (15 trials with 1296 patients); (c) compared to a combination of vasoconstrictors and sclerotherapy (eight trials with 1026 patients); (d) compared to endoscopic variceal ligation (12 trials with 1309 patients). The authors used the risk difference (absolute risk reduction) as their main effect measure. The efficacy of acute sclerotherapy was highest compared to ligation at 95% with a small advantage for ligation (an overtube was used in eight trials) of 2.5% (95% CI 0.4% to 4.6%) ( $p=0.018$ ), but no survival difference. Efficacy of sclerotherapy combined with vasoconstrictors compared to vasoconstrictors alone was 86%, whereas it was 83% for sclerotherapy compared to vasoconstrictors alone. In both these groups sclerotherapy was superior for control of bleeding at, respectively, 16.3% (95% CI 8.7% to 23.9% ( $p<0.0001$ )) and 5.9% (95% CI, 1.5% to 10.3%) ( $p<0.008$ ) with increased survival in the latter. In the combination group of sclerotherapy with vasoconstrictors, the efficacy of sclerotherapy alone was 69%, with the combination superior in controlling bleeding, at 13.2% (95% CI, 8.4% to 18.1%) ( $p<0.0001$ ) but with no survival difference. The authors concluded that the comparison of sclerotherapy across trials demonstrated a problem in defining its real efficacy. The conclusive evidence for substituting banding ligation or the

combination of vasoconstrictors with sclerotherapy as better therapeutic approaches has not been provided in randomised trials. Sclerotherapy remains a gold standard in variceal bleeding but there is scope for further studies of ligation and vasoactive drugs.

In a meta-analysis which combined data from 13 randomised trials, octreotide demonstrated improved control of acute oesophageal variceal bleeding compared to all the alternative therapies combined (relative risk [RR], 0.63; 95% confidence interval [CI], 0.51-0.77); vasopressin or terlipressin (RR, 0.58; 95% CI, 0.42-0.81) or no additional intervention or placebo (among patients who received initial sclerotherapy or banding before randomisation) (RR, 0.46; 95% CI, 0.32-0.67) (Corley 2001). Octreotide had comparable efficacy to immediate sclerotherapy for control of bleeding (RR, 0.94; 95% CI, 0.55-1.62), fewer major complications than vasopressin or terlipressin (RR, 0.31; 95% CI, 0.11-0.87), and a complication profile comparable to no intervention or placebo (RR, 1.06; 95% CI, 0.72-1.55). No specific alternative therapy demonstrated a mortality benefit. The authors of the meta-analysis concluded that the effects of octreotide were comparable to immediate injection sclerotherapy with fewer major complications and that further trials were required to determine the optimal dose, route, and duration of octreotide treatment (Corley 2001).

Because endoscopic therapy and vasoactive drugs are both effective in controlling acute variceal bleeding and preventing recurrent variceal bleeding, it seemed logical to combine injection sclerotherapy with vasoactive drugs in order to achieve an enhanced effect. In a meta-analysis from Madrid assessed whether vasoactive

drugs would improve the efficacy of endoscopic therapy (injection sclerosis or band ligation) in the control of acute variceal bleeding and thus increase survival rates. (Bañares 2002). In this meta-analysis computer databases and scientific meeting abstracts from 1994 to 2001 were used to search for randomised trials that compared the combined use of endoscopic and drug therapy with endoscopic therapy alone in the control of acute variceal bleeding. Eight trials involving 939 patients fulfilled the selection criteria and the following criteria were evaluated by standard meta-analysis methods: initial haemostasis, 5-day haemostasis, 5-day mortality, and adverse events. Combined treatment improved initial control of bleeding (relative risk [RR], 1.12; 95% confidence interval (CI), 1.02-1.23), and 5-day haemostasis (RR, 1.28; 95% CI, 1.18-1.39), with numbers of patients needed to treat (NNT) of 8 and 5, respectively. The difference in favour of combined treatment remained significant when trials that used drugs other than octreotide or that included a low proportion of alcoholic patients (<40%) or high-risk cirrhotic patients (<35%) were excluded. Mortality was not significantly decreased by combined therapy (RR, 0.73; 95% CI, 0.45-1.18). Severe adverse events were similar in both groups. The authors concluded that in patients with acute variceal bleeding, pharmacologic agents improve the efficacy of endoscopic therapy to achieve initial control of bleeding and 5-day haemostasis, yet fail to affect mortality (Bañares 2002).

### **2.6.2 Sclerotherapy compared to surgery**

Four prospective randomised trials conducted in San Francisco, Durban, London and Barcelona have compared injection sclerotherapy with either portacaval shunt surgery or oesophageal transection in the management of patients with acute variceal bleeding.

### **2.6.2.1 Sclerotherapy compared to portacaval shunt**

In a study from San Francisco, 52 patients who had severe cirrhosis and scored Child grade C and had variceal bleeding requiring six or more units of blood were randomly assigned to either injection sclerotherapy or portacaval shunt surgery (Cello 1982). Of 38 pretreatment characteristics, only the frequency of active alcoholism differed significantly between the groups. During the initial hospitalization, the patients in the shunt group required significantly more blood (21.5 +/- 3.1 units) than did those in the sclerotherapy group (12.3 +/- 1.3 units), although the latter had significantly more rebleeding during hospitalisation after the procedure (14 of 28 vs 5 of 24 patients). There was no difference in short-term survival, with 13 patients in the sclerotherapy group discharged alive, compared to 10 patients in the shunt group. Patients were followed for a mean of 263 days after the initial discharge (range: 8 to 1117 days). The sclerotherapy group required significantly more days of hospitalisation for rebleeding, but the study failed to demonstrate any significant difference in long-term survival between the sclerotherapy and shunt groups. Total health-care costs per patient were significantly higher for the shunt group (+23,957 +/- +3,111) than for the sclerotherapy group (+15,364 +/- +2,220). The authors concluded that sclerotherapy was less costly than portacaval shunt and as effective for the treatment of bleeding oesophageal varices due to portal hypertension secondary to severe cirrhosis.

### **2.6.2.2 Sclerotherapy compared to oesophageal transection**

Three prospective randomised controlled trials conducted in Durban, London and Barcelona compared injection sclerotherapy with oesophageal transection in patients with bleeding oesophageal varices (Huizinga 1985, Teres 1987, Burroughs 1989).

In the prospective randomised trial from Durban, 76 high risk patients (Child-Pugh grade B and C) with bleeding oesophageal varices were evaluated and randomised to either transection of the lower oesophagus using an EEA autosuture stapling device or emergency injection sclerotherapy (Huizinga 1985). Thirty-nine patients underwent oesophageal transection and 37 patients were randomised to sclerotherapy and underwent a total of 92 injection procedures (2.4 per patient). The overall perioperative mortality (<30 days) was 29%. The perioperative mortality was 34% in the group of patients who had an oesophageal transection and 24% in those who had injection sclerotherapy ( $\chi^2 = 0.375$ ,  $p > 0.05$ ). Gross ascites, severe encephalopathy and emergency operations were associated with a high mortality in the transection group. Other risk factors such as age and hypersplenism did not influence the outcome in either group. Only patients in Child-Pugh class C died after oesophageal transection, but patients who died in the sclerotherapy group (mainly from recurrent bleeding) included patients from both Child-Pugh class B and C. Early recurrence of nonfatal variceal bleeding occurred in one of 39 patients (2.5%) after oesophageal transection but was evident in 18 of 37 patients (49%) after sclerotherapy ( $\chi^2 = 19.12$ ,  $p < 0.0005$ ), six of whom died. Bleeding did not recur after oesophageal transection during a follow-up period of two years, but a further 22 bleeding episodes occurred in 13 patients receiving sclerotherapy of whom 5 died. Postoperative complications and long term morbidity were similar in the two groups. Including readmissions for bleeding and repeat procedures, the mean hospital stay per patient was shorter for oesophageal transection (14.5 vs 19.1 days) and the requirements for blood were less (1.9 units per patient vs 3.6 units per patient) than for sclerotherapy. The authors concluded that oesophageal transection effectively

protected patients from short term recurrence of bleeding. Preoperative control of gross ascites further reduced the mortality and the authors recommended that comatose patients should be excluded from undergoing an operation. The authors stressed the problem of recurrent variceal bleeding which persisted until variceal eradication had been achieved in patients receiving injection sclerotherapy.

In a clinical trial conducted in Barcelona, 70 consecutive cirrhotic patients with persistent or recurrent variceal bleeding were randomised to compare the efficacy and safety of portacaval shunt (PCS) and oesophageal transection (OT) in patients with low surgical risk, and oesophageal transection and endoscopic sclerotherapy (EIS) in patients with high surgical risk (Teres 1987). To classify the patients into low- and high-risk groups a new scoring system was used, based on an analysis of factors influencing operative mortality in an earlier series of emergency portacaval shunt. Thirty-eight low-risk patients were randomly allocated for treatment with portacaval shunt (19 patients) or stapler transection (19 patients), and 32 high-risk patients for stapler transection (17 patients) or EIS (15 patients). The operative mortality of patients treated by PCS was close to that expected according to retrospective data, indicating that the proposed scoring system was highly discriminant. In low-risk patients, portacaval shunt showed greater haemostatic efficacy and fewer complications than stapler transection. However, hepatic encephalopathy during follow-up was more frequent in the portacaval shunt group and there were no significant differences in operative mortality and long-term survival between the two groups. In high-risk patients, stapler transection and sclerotherapy had a similar haemostatic efficacy, operative mortality and long-term survival. However, sclerotherapy had fewer complications than stapler transection. The

authors recommended stapler transection for low-risk patients and sclerotherapy as an alternative for high-risk patients in the emergency treatment of uncontrolled variceal bleeding.

In the trial conducted in London at the Royal Free Hospital, 101 patients with persistent variceal bleeding were randomised to receive either injection sclerotherapy (n=50) or transection of the lower oesophagus (n=51) using an EEA autosuture staple gun (Burroughs 1989). Patients were enrolled in the study if conservative medical treatment failed to control bleeding within 5 days of the index episode. Four patients assigned to sclerotherapy and 12 assigned to staple transection did not undergo those procedures, but all analyses were made on an intention-to-treat basis. Total mortality did not differ significantly between the two groups; the relative risk of death for staple transection compared with sclerotherapy was 0.88 (95 percent confidence interval, 0.51 to 1.54). Mortality at six weeks was 44% in those assigned to sclerotherapy and 35% in those assigned to staple transection. Complication rates were similar for the two groups. An interval of five days without bleeding was achieved in 88% of those assigned to staple transection and in 62% of those assigned to sclerotherapy after a single injection ( $p < 0.01$ ) and 82% after 3 injections. In only 2 of the 11 patients who received a third sclerotherapy injection was bleeding controlled for more than five days, and 9 died.

At 6 and 12 months, there was no significant difference in survival. The severity of encephalopathy, ascites, prolongation of prothrombin time, and balloon tamponade were independently associated with death at 6 weeks. With surgical intervention, significantly more patients remained free of bleeding for a period of 5 days after

initiation of therapy. Sclerotherapy failed to control bleeding (three sessions) in nine patients, five of whom underwent oesophageal transection. Although bleeding was controlled in all five, only one of these patients survived. The authors concluded that staple transection of the oesophagus was as safe as sclerotherapy for the emergency treatment of bleeding oesophageal varices and recommended that surgical salvage should be used after two injection treatments have failed.

These data support the efficacy of stapling transection of the oesophagus in the management of an episode of variceal bleeding. Previous concerns that transection without devascularisation might be associated with a high rate of rebleeding remain largely unsubstantiated. However, the beneficial effect of reduced rebleeding represents the only major advantage over injection sclerotherapy. It should be stressed that in each of the studies the opportunity to do immediate sclerotherapy at the time of the presenting diagnostic endoscopy was missed in favour of an initial period of observation or vasoconstrictor therapy. This, therefore, represents less than optimum use of injection sclerotherapy and is not standard practice in modern endoscopy units. The possible adverse effect of previous abdominal surgery upon the outcome following liver transplantation applies to oesophageal transection, particularly if a devascularisation has been done. The only role for transection of the oesophagus and gastric devascularisation in current practice is in patients with refractory variceal bleeding who are not suitable for a TIPS stent and who do not have patent venous splanchnic vasculature appropriate for a salvage portacaval shunt.

## **2.7 INJECTION SCLEROTHERAPY TO PREVENT RECURRENT BLEEDING OF OESOPHAGEAL VARICES**

### **2.7.1 Sclerotherapy versus conservative treatment**

The role of emergency endoscopic injection sclerotherapy to control acute variceal bleeding and followed by repeated long term injection sclerotherapy to thrombose and eradicate residual oesophageal varices and thus prevent recurrent variceal bleeding has been investigated in eleven prospective randomised controlled trials (Barsoum 1982, Terblanche 1983, EVASP 1984, Westaby 1985, Soderlund 1985, Korula 1985, Burroughs 1985, Paquet 1985, Rossi 1991, Gregory 1994, Wu 2007)

In a study from Cairo 100 patients with bleeding oesophageal varices were randomized into two treatment groups after resuscitation (Barsoum 1982). One group was managed by tamponade only (group 1); the other group (group 2) was treated by endoscopic injection of oesophageal varices. The patients in group 2 were further subdivided into 25 patients (group 2a), who had tamponade applied immediately after sclerotherapy, and 25 patients (group 2b), who had sclerotherapy without subsequent tamponade. Injection of varices controlled the acute bleeding episode more effectively than tamponade (74% in group 2 vs 42% in group 1). There was no significant difference in the overall mortality rate of the two groups, but group 2 had a significantly higher proportion of Child's grade C patients (38/50 vs 29/50 = 76% vs 58%). If only Child's grade C patients are considered, 16 of 29 (55%) died in group 1, whereas 12 of 38 (32%) died in group 2 ( $p < 0.05$ ). Tamponade applied after sclerotherapy had no demonstrable effect on the outcome of sclerotherapy. The long term follow-up of patients (maximum 4 years) showed that recurrence of bleeding

was less in the sclerotherapy group (8.1%) than in the tamponade only group (27.6%;  $p < 0.05$ ).

In a landmark study published in the Lancet, the Cape Town group evaluated the long term role of sclerotherapy in the management of patients after oesophageal variceal bleeding by comparing repeated sclerotherapy using a rigid oesophagoscope in 37 patients with a control group of 38 patients who received conventional medical management (Terblanche 1983). Varices were eradicated in 21 of 22 (95%) patients analysed in the sclerotherapy group, but recurred in 13 of 21 patients at an average of 21.5 months. Varices persisted in 13 of 14 surviving control group patients. The sclerotherapy patients had fewer recurrent bleeds than control patients (43 versus 73) and most of the bleeds occurred before variceal eradication and were mild. However, there was no difference in survival in the two groups. The commonest cause of death was liver failure which occurred in 37 patients. Thirty two complications occurred in 24 patients during 258 injections. Repeated sclerotherapy failed to improve survival in this trial, although varices were eradicated and recurrent variceal bleeds were prevented with adequate follow-up. An important consideration in the methodology of the study was that the control group received acute injection sclerotherapy whenever further variceal bleeding occurred. This trial therefore in reality compared acute control of variceal bleeding followed by repeated sclerotherapy to eradicate varices with sclerotherapy “on demand” whenever variceal rebleeding occurred.

In a prospective randomised multicentre trial conducted by the members of the Copenhagen oesophageal varices sclerotherapy project in Denmark, 187 unselected patients with cirrhosis and bleeding oesophageal varices were randomly

assigned to medical treatment including balloon tamponade or to medical treatment supplemented with intensive, paravariceal sclerotherapy (EVASP 1984). Follow-up period ranged from 9 to 52 months. The overall mortality in the sclerotherapy group (hazard) was 76% (95% confidence limits, 54-107%) of that in the medical-regimen group. The relative mortality in the sclerotherapy group, determined by stratifying according to degree of encephalopathy and ascites, was 63% of that in the medical-regimen group (95% confidence limits, 44-91%). The main effect of sclerotherapy may be a reduction of long-term mortality, which after day 40 was only 43% (95% confidence limits, 23-79%) of that in the medical-regimen group. Sclerotherapy had no significant influence on the initial haemorrhage as judged from the duration of bleeding or of balloon tamponade, the number of blood transfusions needed, or immediate mortality. Forty-five patients in the sclerotherapy group had 64 episodes of recurrent bleeding, as compared with 138 episodes among 51 patients in the medical-regimen group. This difference was due to a pronounced reduction of rebleeding after day 40 in the sclerotherapy group. The authors concluded by recommending sclerotherapy for patients with cirrhosis who have bled from oesophageal varices.

In a prospective controlled trial conducted in Stockholm, 107 cirrhotic patients with major variceal bleeding were randomised to either a control group who received conservative therapy which included vasopressin and balloon tamponade or a treatment group who received endoscopic variceal injection sclerotherapy for acute bleeding and rebleeding. (Soderlund 1985). Variceal eradication was achieved in 22 variceal sclerotherapy patients in the first year after a median of 6 months and 5 sclerotherapy sessions, and in 7 variceal sclerotherapy patients after 21 months and

9 sclerotherapy sessions. Eleven variceal sclerotherapy patients and 11 controls rebled on 30 and 45 occasions during a total follow-up time of 1364 and 696 months and 0.0220 and 0.0647 bleeds per patient-month, respectively ( $p = 0.098$ ). Eight variceal sclerotherapy patients experienced 12 variceal bleeds, 11 controls had 39 bleeds due to varices, 0.0088 and 0.0560 bleeds per patient-month ( $p = 0.016$ ), respectively. Five variceal sclerotherapy patients had recurrent varices on nine occasions with five bleeding episodes at a median of 13 months after completion of the initial serial variceal sclerotherapy. Re-eradication was achieved with a median of three variceal sclerotherapy sessions during 3 months, but three patients had a second variceal recurrence 14-24 months later, successfully treated with one variceal sclerotherapy sessions. There was no difference in survival (Soderlund 1985).

In a prospective randomised trial conducted in London, the group from Kings College Hospital randomised 107 patients with cirrhosis and variceal bleeding to receive either endoscopic injection sclerotherapy or conservative medical therapy (Macdougall 1982). In the sclerotherapy group 22 (43%) of the 51 patients had recurrent variceal bleeding while undergoing variceal sclerotherapy, but in only 4 did bleeding occur after the varices had been obliterated. This contrasted with recurrent bleeding in 42 (75%) of the 56 patients receiving standard medical management which was a significant difference. The overall risk of bleeding per patient-month of follow-up was reduced threefold with sclerotherapy. Of 22 patients followed up for one year after obliteration of varices, 14 had no evidence of recurrent varices and, by cumulative life-analysis tables, survival was shown to be significantly improved in the sclerotherapy group.

In a subsequent analysis the same group published the long-term results of the earlier report published in the Lancet (Westaby 1985). The 116 patients (56 sclerotherapy, 60 control group) entered into the completed controlled trial of endoscopic variceal sclerotherapy (median follow-up: 37 months; range: 19 to 68 months) showed a total of 18 deaths in the sclerotherapy group, including five from variceal bleeding compared with 32 deaths in the control group ( $p < 0.01$ ), of whom 25 were due to variceal bleeding ( $p < 0.001$ ). Survival as assessed by cumulative life analysis was significantly better in those treated by sclerotherapy ( $p < 0.001$ ). Both the cumulative proportion of patients rebleeding and the total number of episodes of variceal bleeding were also significantly less in the sclerotherapy group ( $p < 0.01$ ). Recurrence of varices was observed in 27 of 45 patients in whom variceal obliteration was initially observed at a median of 11 months (range: 2 to 27 months) later, although in only 12 of whom did bleeding recur and caused the death in one (Westaby 1985).

In a prospective, randomised controlled trial of chronic oesophageal variceal sclerotherapy conducted at the University of Southern California in Los Angeles over a 38-month period 120 patients were randomised after a variceal bleed. Sixty three patients were randomised to endoscopic injection sclerotherapy and 57 to the control group (Korula 1985). Mean follow-up was similar in both groups (oesophageal variceal sclerotherapy, 12.5 +/- 8.8 months; control, 14.9 +/- 6.6 months). Twenty-one percent of the patients in each group were lost to follow-up. Oesophageal variceal sclerotherapy decreased rebleeding as evidenced by a decrease in the mean bleeding risk factor, transfusion requirement and by an increase in bleeding free interval; differences between the treated and control groups in these parameters

were especially significant after variceal obliteration. A high incidence of asymptomatic ulceration and low frequency of strictures were notable effects of the oesophageal variceal sclerotherapy. Cumulative life table analysis revealed no differences in survival between oesophageal variceal sclerotherapy and control groups. However, when patients who received portal-systemic shunt surgery (oesophageal variceal sclerotherapy, 6%; control, 28%) were removed from the analysis at the time the shunt surgery was performed (defining the shunt as an endpoint, a significant difference in survival ( $p < 0.05$ ) in favour of oesophageal variceal sclerotherapy was seen.

In a prospective randomised controlled clinical trial performed at the Heinz Kalk Clinic in Bad Kissingen in West Germany 43 consecutive cirrhotic patients with endoscopically proven bleeding oesophageal varices were randomly selected to have either oesophageal tamponade with a Sengstaken-Blakemore tube ( $n=22$ ), or endoscopic sclerotherapy of the oesophageal varices ( $n=21$ ) (Paquet 1985). The two groups were similar in demographic, clinical and laboratory data. Bleeding was controlled with a Sengstaken-Blakemore tube in 16 of 22 patients (73%) and by endoscopic sclerotherapy in 20 of 21 (95%) patients. Among those controlled by the Sengstaken-Blakemore tube, seven (44%) rebled and three (43%) were again controlled by the Sengstaken-Blakemore tube; in the endoscopic sclerosis group, four (20%) rebled and three (75%) were controlled. Thus, bleeding was definitively controlled in 52% of patients and 66% of bleeding episodes in the Sengstaken-Blakemore tube group and in 90% of patients and 92% of bleeding episodes in the endoscopic sclerotherapy group. The definite control of bleeding was significantly better in the endoscopic sclerotherapy group ( $p < 0.01$ ). The Sengstaken-Blakemore

tube patients received no definitive therapy after bleeding had been controlled. Within 30 days, six patients (27%) in the Sengstaken-Blakemore tube group had died compared to 2 (10%) in the endoscopic sclerotherapy group which is statistically significant ( $p < 0.01$ ) in favour of endoscopic sclerotherapy. The frequency of complications was similar in the two groups. Endoscopic sclerotherapy patients received serial endoscopic sclerosis after bleeding had been stopped during the whole period of follow-up. After 6 months 11 patients in the Sengstaken-Blakemore tube group had died (55%) compared to 3 patients (16%) in the endoscopic sclerotherapy group. Cumulative survival was statistically better in the endoscopic sclerotherapy group after 6 months ( $p < 0.01$ ) and after 3 years of follow-up ( $p < 0.001$ ). Survival was related to Child grade on admission. This trial showed that endoscopic sclerotherapy was effective and superior to using a Sengstaken-Blakemore tube in stopping active bleeding from oesophageal varices and was significantly superior to using a Sengstaken-Blakemore tube in reducing short and long-term mortality (Paquet 1985).

In a trial from the Royal Free Hospital in London, 206 cirrhotic patients with bleeding oesophageal varices were randomised to either weekly sclerotherapy ( $n=103$ ) or no injection ( $n=103$ ) during a 62 month period (Burroughs 1985). The latter group were given sucralfate 1g qid. A standard protocol was used to treat all bleeds and randomisation took place after a 5 day bleed-free interval from admission stratified by the initial treatment used. Trial groups were matched for age, gender, aetiology of cirrhosis, previous bleeding, treatment variables at index bleed and Pugh's grade A, B and C (sclerotherapy 35; 42; 26, sucralfate 22; 57; 24). Separate episodes of rebleeding were defined by a bleed-free interval of 5 days and were analysed

regardless of severity or source. Deaths occurred in 55 (53%) of sucralfate group and in 48 (47%) of the sclerotherapy patients (log rank test  $p = 0.49$ ). Oesophageal and gastric variceal rebleeding occurred in 59% in the sucralfate group versus 56% in sclerotherapy patients (log rank test  $P = 0.46$ ). Total number of variceal rebleeds were 183 in the sucralfate group and 130 in patients receiving sclerotherapy. However, a rebleeding index evaluating all sources and taking into account intervals without rebleeding was not significantly different. In each trial group 3% of patients had liver transplants, 7% had shunts and 1% had a devascularisation operation. The authors concluded that long-term sclerotherapy did not significantly benefit patients when emergency treatment for bleeding was kept constant. The reduction in variceal bleeding episodes is marginal; 50 episodes for 100 patients treated over 5 years (Burroughs 1985).

A prospective randomised controlled study conducted in the Service d'Hépatogastroentérologie, Centre Hospitalier Universitaire, Angers, France, evaluated the effectiveness of sclerotherapy compared to a control group in the prevention of variceal rebleeding in alcoholic cirrhotic patients (Rossi 1991). In the 79 patients, the distribution according to Child-Pugh classification was: A, 22%; B, 40%; and C, 38%. Sclerotherapy was performed weekly using 1% polidocanol. End points were rebleeding or death. During the mean follow up of 19 +/- 16 months, 43 patients bled and 22 patients died. The cumulative percentages of patients free of rebleeding at 1 year were: sclerotherapy, 64% (95% CI: 45-82); control, 54% (95% CI: 36-71); these differences did not reach statistical significance. The cumulative percentages of patients alive at 1 year were: sclerotherapy, 79% (95% CI: 58-91); control, 81% (95% CI: 60-93); these differences were not statistically significant. Alcohol

withdrawal, which occurred in 66% of patients, was an independent predictive factor associated with a decreased risk of rebleeding or death.

Sclerotherapy and sham-sclerotherapy were compared in male alcoholic patients with cirrhosis and bleeding oesophageal varices in a prospective, single-blind, randomised clinical trial which entered 253 patients at 12 Veterans Affairs Medical Centres (Gregory 1994). Patients were either actively bleeding from oesophageal varices at randomisation or had a history of such bleeding. Patients were treated either by endoscopy with sham-sclerotherapy or endoscopy with sclerotherapy at randomisation, and then subsequently at 4 to 6 days, 9 to 11 days, 1 month, 3 months and every 3 months for 2 years and followed for the remainder of the study period. Of the patients randomised, 131 were assigned to sham-therapy and 122 were assigned to sclerotherapy. At entry the two patient groups were comparable. The upper gastrointestinal rebleeding rates during the study were 101 and 66 per 100 person years of follow-up in sham-therapy and sclerotherapy, respectively (RR, 1.54; 95% CI, 1.06 to 2.22;  $p = 0.01$ ). A significantly higher number of episodes were attributable to oesophageal varices in the sham-therapy group (112 vs 52;  $p = 0.005$ ). Seventy-four sham-therapy patients (56%) and 77 sclerotherapy patients (63%) died ( $p = 0.54$ ; RR, 0.91; 95% CI, 0.66 to 1.25). The mean transfusion requirement was higher in the sham-therapy group (16.0 units vs 9.4 units;  $p=0.002$ ) and more patients in this group required shunt surgery (18 vs 5;  $p=0.005$ ). The rate of recurrent bleeding, number of episodes of bleeding due to oesophageal varices, mean transfusion requirement, and need for shunt surgery were significantly higher in the sham-sclerotherapy group of patients. Mortality rates were the same for both groups.

In a study from Taipei, Taiwan, fifty patients with repeated bleeding from oesophageal varices were entered into a prospective randomised controlled trial (Wu 2007). Twenty five patients were randomised to a sclerotherapy arm and 25 patients to a control arm. Thirty-seven of the 50 patients had postnecrotic cirrhosis and 13 patients had primary hepatocellular carcinoma. A combined intra-variceal and para-variceal injection technique was used in the sclerotherapy group. In all 25 sclerotherapy patients (100%) haemostasis was successful, which was a statistically significant success rate compared to the control group (52%) ( $p < 0.01$ ). In the sclerotherapy group 5 of the 25 patients (20%) rebled, which was less than the 12 patients (48%) who had either continued bleeding (7) or rebleeding (5) in the control group ( $p < 0.05$ ). Four patients (16%) in the sclerotherapy group died of erosive gastritis with massive bleeding compared to 8 deaths (32%) in the control group who had uncontrolled oesophageal variceal bleeding. The authors concluded that endoscopic sclerotherapy was an effective method for arresting bleeding from oesophageal varices and for decreasing the rebleeding rate.

These eleven trials included and randomised a total of 1,336 patients. In four trials, emergency sclerotherapy was used to treat variceal rebleeding in the sclerotherapy arm of the trial but not in the control arm. The incidence of rebleeding was reduced in seven studies in the sclerotherapy treated patients. Mortality was reduced in the sclerotherapy treated group in six studies, was no different in four and increased in another. On an individual basis, all the trials showed a benefit for injection sclerotherapy in terms of recurrent bleeding.

Meta-analysis of seven of the long-term studies showed a significant 25% overall reduction in mortality in patients receiving endoscopic sclerotherapy, compared with medical management (D'Amico 1995). Cumulative significant non-bleeding complications associated with sclerotherapy in these trials, however, totalled 23% per patient. Two meta-analyses have confirmed a significant benefit in favour of injection sclerotherapy with regard to recurrent bleeding and survival and both these endpoints improved by 50% in the sclerotherapy treated groups. (Infante-Rivard 1989, D'Amico 1995)

Despite the evidence offered by meta-analyses in favour of long-term injection sclerotherapy, an important area of controversy remains concerning the treatment permitted for patients in the control groups who presented with recurrent variceal bleeding. In most trials, this treatment was restricted to conservative measures, such as vasoconstrictor drugs or balloon tamponade. All the trials which showed a significant survival benefit for injection sclerotherapy used a protocol restricted to conservative treatment. In contrast, no survival benefit was observed in the trials in which a single session of injection sclerotherapy was permitted for recurrent bleeding episodes in the control groups. It has therefore been suggested that restricting sclerotherapy to episodes of recurrent bleeding alone has the same survival advantage as a long-term regimen. The available data cannot definitively answer this question. If a survival benefit does not accrue from long-term injections sclerotherapy, justification for its use would depend on the extent of the reduction in the frequency of recurrent bleeding and associated cost analysis.

## 2.7 INJECTION SCLEROTHERAPY TO PREVENT RECURRENT BLEEDING OF OESOPHAGEAL VARICES

### 2.7.2 Sclerotherapy compared to beta-blockers

Seven meta-analyses have shown that beta-blockers decrease the risk of recurrent bleeding in patients with cirrhosis (Pagliaro 1989, Poynard 1987, Hayes 1990, Pagliaro 1990, Pignon 1988, Bernard 1994, D'Amico 1995), although only two of these studies showed an increase in long-term survival (Hayes 1990, Bernard 1994). Two meta-analyses have shown that endoscopic sclerotherapy significantly decreases the risk of variceal rebleeding in patients with cirrhosis (Pagliaro 1989, D'Amico 1995) and three meta-analyses have shown an improvement in long-term survival (Pagliaro 1989, D'Amico 1995, Infante-Rivard 1989). In the randomised clinical trials which have compared the efficacy of beta-blockers and sclerotherapy (Fleig 1987, Dollet 1988, Alexandrino 1988, Westaby 1990, Andreani 1990, Martin 1991, Rossi 1991, Dasarathy 1992, Teres 1993), three have demonstrated the superiority of sclerotherapy in preventing rebleeding (Alexandrino 1988, Dasarathy 1992, Teres 1993), and one has shown a significant difference in survival in favour of sclerotherapy (Dasarathy 1992). In the two meta-analyses which compared beta-blockers and endoscopic sclerotherapy and their effect on the risk of rebleeding and survival (Pagliaro 1989, D'Amico 1995), only one showed a significant difference in favour of sclerotherapy for rebleeding (D'Amico 1995), and no difference was found in survival (Pagliaro 1989, D'Amico 1995).

In the most recent assessment Bernard and her colleagues from Hôpital Pitié-Salpêtrière in Paris performed a meta-analysis of nine randomised trials which compared the effects of propranolol and sclerotherapy in the prevention of

rebleeding and on survival in patients with cirrhosis and bleeding oesophageal varices (Bernard 2007). Five end points were assessed in the meta-analysis: the overall rebleeding rate, oesophageal variceal rebleeding, overall death, death due to bleeding, and adverse events. Analyses were performed according to an intention-to-treat design. For each end point, heterogeneity and treatment efficacy were assessed by Der Simonian and Peto calculations. When a significant difference was observed, sensitivity analyses were performed by successive stratification according to treatment duration, type of publication, severity of cirrhosis, and methodological quality. The authors found that the mean percentage of patients free of rebleeding, the mean survival rate and the mean percentage of patients free of death from bleeding were not significantly different between patients treated with propranolol and those treated by sclerotherapy. The mean percentage of patients free of variceal rebleeding was 39% in propranolol group and 55% in sclerotherapy group (mean difference: 17%, 95% confidence interval: 9-25%,  $p < 0.001$ ). The mean percentage of patients free of adverse events was significantly higher in the propranolol group than in the sclerotherapy group (mean difference: 22%, 95% confidence interval: 6-38%,  $p < 0.007$ ). The authors concluded that in patients with cirrhosis and oesophageal varices, endoscopic sclerotherapy was more effective than propranolol in preventing variceal rebleeding, but that the incidence of adverse events was significantly higher with sclerotherapy. There was no difference in survival between the treatments.

## **2.7 INJECTION SCLEROTHERAPY TO PREVENT RECURRENT BLEEDING OF OESOPHAGEAL VARICES**

### **2.7.3 Sclerotherapy versus sclerotherapy plus beta-blockers**

When used without adjuvant vasoactive drugs, endoscopic sclerotherapy controls bleeding in 80% to 90% of patients with acutely bleeding varices. Vasoactive drugs, such as somatostatin and terlipressin, have been shown to be as effective as endoscopic sclerotherapy in controlling variceal bleeding and preventing early rebleeding (Banares 2002). The question arises whether adjuvant drugs would improve the efficacy of endoscopy without enhancing adverse events. The goal of combining both types of therapy would be to add the portal pressure lowering effect of vasoactive drugs to the local haemostatic effects of injection sclerotherapy. To answer this question several different vasoactive drugs have been tested in randomised trials. Whereas drugs improved the efficacy of endoscopic therapy in the control of bleeding in each trial, the impact on overall survival has varied among studies.

In a systematic review and meta-analysis from derived data Banares and his colleagues from Hospital General Gregorio Marañón and the Universidad Complutense in Madrid, assessed whether vasoactive drugs improved the efficacy of endoscopic injection sclerotherapy in the control of acute variceal bleeding and thus increased survival rates (Banares 2002). The authors searched computer databases and scientific meeting abstracts from 1994 to 2001 for all randomised trials which compared the combined use of endoscopic and drug therapy with endoscopic

therapy alone to control acute variceal bleeding. Eight trials involving 939 patients fulfilled the selection criteria. The end-points evaluated by standard meta-analysis methods were initial control of bleeding, 5-day haemostasis, 5-day mortality, and adverse events. Combined treatment improved initial control of bleeding (relative risk [RR], 1.12; 95% confidence interval, 1.02-1.23), and 5-day haemostasis (RR, 1.28; 95% CI, 1.18-1.39), with numbers of patients needed to treat (NNT) of 8 and 5, respectively. The difference in favour of combined treatment remained significant when trials which used drugs other than octreotide or those which included a low proportion of alcoholic patients (<40%) or high-risk cirrhotic patients (<35%) were excluded. Mortality was not significantly decreased by combined therapy (RR, 0.73; 95% CI, 0.45-1.18). Severe adverse events were similar in both groups. The authors concluded that in patients with acute variceal bleeding, pharmacologic agents improved the efficacy of endoscopic therapy in achieving initial control of bleeding and 5-day haemostasis, yet failed to improve survival (Banares 2002).

In a further meta-analysis which included more recent trials and more patients, Gonzalez and colleagues from Hospital Universitario Ramón y Cajal in Madrid assessed whether the combination of endoscopic and drug therapy prevented overall and variceal rebleeding and improved survival better than either therapy alone (Gonzalez 2008). The authors searched Medline, Embase, the Cochrane Central Register of Controlled Trials, the Cochrane Database of Systematic Reviews, and conference proceedings from 1996 to 2007 to identify randomised trials which compared endoscopic plus beta-blocker therapy with either therapy alone. In the analysis two reviewers independently extracted data on interventions and the primary study outcomes of overall rebleeding and mortality. Meta-regression

and stratified analysis were used to explore heterogeneity. Twenty three trials which included 1860 patients met the inclusion criteria. The authors found that combination therapy reduced overall rebleeding more than endoscopic therapy alone (pooled relative risk, 0.68 [95% CI, 0.52 to 0.89];  $I^2 = 61\%$ ) or beta-blocker therapy alone (pooled relative risk, 0.71 [CI, 0.59 to 0.86];  $I^2 = 0\%$ ). Combination therapy also reduced variceal rebleeding and variceal recurrence. Reduction in mortality from combination therapy did not statistically significantly differ from that from endoscopic (Peto odds ratio, 0.78 [CI, 0.58 to 1.07) or drug therapy (Peto odds ratio, 0.70 [CI, 0.46 to 1.06]). Effects were independent of the endoscopic procedure (injection sclerotherapy or banding). No trial-level variable associated with the effect was identified through metaregression or stratified analysis. The authors acknowledged that although a statistically significant heterogeneity in trial quality and evidence for selective reporting and publication bias were found, the meta-analysis supported the conclusion that a combination of endoscopic and drug therapy reduced overall and variceal rebleeding in cirrhosis more than either therapy alone (Gonzalez 2008).

The authors indicate that their findings suggest that a combination of endoscopic and drug therapy is better than either treatment alone in the prevention of overall and variceal rebleeding in patients with cirrhosis and an initial variceal bleeding event. The effect of combination therapy was observed regardless of whether injection sclerotherapy or variceal banding was used, although variceal banding has been shown to be safer and more effective than sclerotherapy for prevention of variceal rebleeding (Tait 1999). The authors report that meta-regression and stratified meta-analyses based on a priori, trial-level covariates showed little association with the effect of combination therapy on preventing variceal rebleeding or mortality and

could not explain the statistical heterogeneity observed for rebleeding outcomes. Combination therapy also reduced mortality; however, the effect was more modest than that for rebleeding prevention and not statistically significant. Sparse mortality data probably contributed to the apparent lack of effect on mortality rate; deaths related to acute variceal bleeding episodes have decreased over the past 2 decades whereas causes of death unrelated to portal hypertension and varices, such as hepatocellular carcinoma, have increased and are unlikely to be modified by endoscopic or drug therapy (Gonzalez 2008).

The advantages of adjunctive drug or endoscopic therapy in prevention of rebleeding should be weighed against the potential for more adverse events. Patient withdrawals because of side effects occurred almost exclusively in the beta-blocker group. However, the quality of adverse event reporting varied and often quantified overall rather than per-patient events. Also, most trials did not distinguish serious from nonserious adverse events and the trials were not double-blinded for both drug and endoscopic therapies. The authors acknowledge that their meta-analysis has several limitations. The quality of the studies varied. Randomisation was adequate in all trials; however, 7 papers did not explicitly state whether analysis of data adhered to the intention-to-treat principle which could lead to overestimation of treatment effect in these trials, and the quality of 4 of the 5 trials reported as abstracts could not be assessed. Analyses did not identify an association between components of quality and rebleeding risk, and the effect size in favor of combination therapy remained statistically significant when trials which were reported as abstracts were excluded. In addition, publication bias might have accounted for some of the effect the authors observed. Smaller trials are, in general, analysed with

less methodological rigor than larger studies and an asymmetrical funnel plot suggests that selective reporting may have led to an overestimation of effect sizes in small trials. The meta-analysis supports combining endoscopic and beta-blocker therapy to prevent variceal rebleeding in patients with cirrhosis. The effect of combination therapy on survival remains uncertain, and the findings in this meta-analysis cannot be applied to patients different from those in the trials, such as those with noncirrhotic variceal bleeding, those already receiving beta-blockers, and those who have received endoscopic intervention or had drug therapy as primary treatment. Further studies are needed to define subgroups of patients more likely to benefit from combination therapy (Gonzalez 2008).

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## 2.7 INJECTION SCLEROTHERAPY TO PREVENT RECURRENT BLEEDING OF OESOPHAGEAL VARICES

### 2.7.4 Comparative efficacy of endoscopic variceal treatment

#### (i) Endoscopic Variceal Ligation compared with Endoscopic Sclerotherapy:

Data from thirteen peer reviewed prospective randomised controlled trials comparing the efficacy and complications of endoscopic variceal ligation (EVL) and endoscopic injection sclerotherapy (EIS) have been published in full and are summarised in Table 2.7.1. The first study by Stiegmann et al. found band ligation to have improved survival and fewer complications (Stiegmann 1992). Laine reported a significant reduction in local complications but no difference in rebleeding or mortality (Laine 1993). Gimson reported that band ligation obliterated the varices more rapidly and reduced the incidence of rebleeding but without affecting mortality or complications (Gimson 1993). Lo documented that ligation reduced rebleeding, mortality, and complications and achieved obliteration more rapidly (Lo 1995). Hou found that EVL was superior to EIS in reducing rebleeding and complications but not mortality (Hou 1995). Eradication was achieved in fewer treatment sessions in the trials reported by Sarin and Baroncini with clear benefit in terms of fewer procedure-related complications (Baroncini 1997, Sarin 1997). Avgerinos found that EVL eradicated varices more swiftly than EIS and with fewer complications (Avgerinos 1997). Masci et al recorded significantly more major complications with EIS (36% vs 10%) (Masci 1999).

de la Pena et al found similar rates of variceal eradication, but eradication was accomplished sooner and with fewer complications in patients undergoing EVL (de la Pena 1999). In 84 patients with schistosomal and post-hepatic cirrhosis, Fakhry et

al. required significantly less treatment sessions to eradicate varices and with fewer complications with EVL (Fakhry 2000). In 73 adult patients with bleeding oesophageal varices due to extrahepatic portal vein obstruction Zargar et al. found that EVL achieved variceal eradication with significantly fewer endoscopic sessions and less complications than EIS (Zargar 2005).

A meta-analysis of the seven initial randomised trials concluded that EVL reduced the rebleeding rate (OR 0.52; 95% CI, 0.37 - 0.74), mortality rate (OR 0.67; CI, 0.46 - 0.98), and rate of death due to bleeding (OR 0.49; CI 0.24 - 0.996) compared with EIS (Laine 1995). Oesophageal strictures occurred less frequently with EVL (OR 0.10; CI 0.03 - 0.29). The number of endoscopic treatment sessions required to achieve variceal obliteration was lower with EVL than with EIS. On the basis of lower rates of rebleeding, mortality, and complications and the need for fewer endoscopic treatments, EVL should be considered the endoscopic treatment of choice for patients with bleeding oesophageal varices (Laine 1995).

**(ii) EVL compared with combination therapy (EVL plus EIS):**

EIS of large oesophageal varices may be technically demanding and generally requires greater sclerosant volumes, more commonly results in needle puncture bleeding, and requires more endoscopy sessions with an increased risk of serious complications (Krige 1999). In contrast, banding is ideally suited to large varices but becomes progressively more difficult with each subsequent session as varices reduce in size and less variceal tissue is available to trap in the **O** rings (Tait 1999). The combination of EVL and small volume EIS thus has the potential advantage of augmenting the benefits of both techniques by achieving more rapid variceal

eradication and less chance of variceal recurrence, thus reducing the likelihood of later rebleeding.

**(a) Synchronous combination (EVL + EIS) therapy:**

The combination of EVL and synchronous EIS should theoretically achieve more rapid variceal eradication, as the sclerosant is injected into a stagnant varix above the ligation site. Laine et al compared EVL alone with EVL plus sclerotherapy (EVL/EIS) in 41 patients (Laine 1996). Twenty-one patients randomised to EVL/EIS had their oesophageal varices ligated then 1 ml of sclerosant (1.5% sodium tetradecyl sulfate) injected into the varix immediately above the ligature. However, the anticipated benefits were not realised in this study which reported similar eradication, rebleeding and deaths rates in the two groups (Table 2.7.2). More treatment sessions (rather than fewer) were required to achieve eradication in the combined treatment arm, which caused more complications than EVL alone. Similar results were reported by Saeed et al (1997), Umehara et al (1999), Al Traif et al (1999), Djurdjevic et al (1999), Argonz et al (2000) and Hou et al (2001) that control of acute bleeding, rebleeding rates, variceal eradication rates, and mortality were similar in the two treatment groups (Table 2.7.2). However, more endoscopy sessions were required to achieve eradication with combination therapy, which was associated with a higher incidence of deep mucosal ulceration, dysphagia and oesophageal strictures.

A meta-analysis (Singh 2002) found no significant differences between EVL and EIS combined versus EVL alone in terms of oesophageal rebleeding (RR = 1.05; 95% CI = 0.67-1.64;  $p = 0.83$ ), death (RR = 0.99; 95% CI = 0.68-1.44;  $p = 0.96$ ) or number of

endoscopic sessions to variceal obliteration (RR = 0.23; 95% CI = 0.055-0.51;  $p = 0.11$ ). However, the incidence of oesophageal strictures was significantly higher in the EVL plus EIS group than in the EVL alone group. The meta-analysis of these studies suggests that little is to be gained by the addition of low dose sclerotherapy to standard ligation techniques. Based on the available evidence, synchronous treatment with EVL and EIS provides no additional benefit and is associated with higher patient morbidity.

**(b) Sequential combination (EVL + EIS) therapy:**

Recognising the technical limitations of EVL and synchronous EIS, Bhargava and Pokharna (1996) adopted a more pragmatic approach to combination therapy (Table 3). Patients were randomised to either EVL alone, or to the combination of EVL and sequential EIS. Combination therapy used repeated EVL until the varices were reduced in size to grade II, followed by weekly small volume sclerotherapy to achieve complete eradication. Overall the combined treatment cohort required more endoscopic sessions ( $5.9 \pm 2.3$  vs.  $4.3 \pm 1.8$ ;  $P < 0.05$ ), but re-bleeding rates (19% vs 22%), and complication rates were similar in the two groups. This study suggested that a staged approach to combination therapy was better, as it achieved 100% variceal eradication without the associated high rate of iatrogenic complications normally associated with EIS. In their study Lo et al (1998) found that eradication and number of sessions needed were similar in both groups. However, the mortality (2.7% vs 8.6%), rebleeding (8% vs 31%) and variceal recurrence (14% vs 43%) rates were lower with combination therapy than with EVL alone. Masumoto (1998) found no difference in their study.

**(b) EIS alone compared to combined EVL and EIS therapy:**

Iso et al (1997) compared EIS alone with a step-wise combination of EVL as initial treatment followed by weekly EIS (Table 2.7.4). There were significantly less iatrogenic complications with the combined EVL/EIS strategy. Garg et al (1999) found that more complications (20% vs 3%) and rebleeding (16% vs 3%) occurred with sclerotherapy alone. Nishikawa (1999) found the number of treatment sessions for eradication was significantly less (2.3 vs 3.9,  $p<0.001$ ) for EVL and EIS as was total sclerosant used. In the study by Shigemitsu (2000) eradication was achieved with significantly less sclerosant in the combined EVL/EIS group (17 vs 25ml,  $p<0.05$ ).

**Table 2.7.1 Randomised trials comparing endoscopic sclerotherapy with band ligation**

Author (year) (total number)	Patients	Group	Sessions	Rebleed (%)	Variceal bleeding	Comp (%)	Recurrence (%)	Eradication (%)	Survival (%)
Stiegmann (1992) (n = 129)	65	EIS	5± 2	48	52	<b>22</b>	50	56	55
	64	EVL	4±2	36	48	<b>2</b>	33	55	72
Laine (1993) (n = 77)	39	EIS	<b>6.2±0.4</b>	44	31	<b>56</b>	na	69	85
	38	EVL	<b>4.1±0.3</b>	26	24	<b>24</b>	na	59	89
Gimson (1993) (n = 103)	49	EIS	<b>4.90</b>	53	51	57	na	71	37
	53	EVL	<b>3.40</b>	30	24	67	na	82	52
Lo (1995) (n = 120)	59	EIS	<b>6.5±1.2</b>	51	36	<b>19</b>	na	63	<b>68</b>
	61	EVL	<b>3.8±0.4</b>	33	13	<b>3</b>	na	74	<b>84</b>
Hou (1995) (n = 134)	67	EIS	<b>4.6±1.6</b>	33	43	<b>22</b>	<b>30</b>	79	84
	67	EVL	<b>3.5±1.6</b>	18	38	<b>5</b>	<b>48</b>	87	79
Sarin (1997) (n = 95)	48	EIS	<b>5.2±1.8</b>	21	na	<b>50</b>	<b>8</b>	92	94
	47	EVL	<b>4.1±1.2</b>	6	na	<b>45</b>	<b>29</b>	96	94
Baroncini (1997) (n = 111)	54	EIS	<b>4.0±0.1</b>	19	30	<b>31</b>	<b>13</b>	93	78
	57	EVL	<b>3.5±0.1</b>	16	22	<b>11</b>	<b>30</b>	93	79
Avgerinos (1997) (n = 77)	40	EIS	<b>5.8 ±2.7</b>	47	25	<b>60</b>	44	97	80
	37	EVL	<b>3.7 ±1.9</b>	27	14	<b>35</b>	31	93	78
Hou(1999) (n = 168)	84	EIS	5.1±2.2	38	32	na	na	86	na
	84	EVL	3.7±1.7	24	43	na	na	88	na
Masci (1999) (n = 100)	50	EIS	<b>5.3</b>	<b>42</b>	10	38	27	82	na
	50	EVL	<b>3.4</b>	<b>12</b>	14	18	32	88	na
de la Pena (1999) (n = 88)	46	EIS	<b>5.3±1.6</b>	<b>50</b>	<b>30</b>	<b>41</b>	28	71	78.
	42	EVL	<b>6.6±2.4</b>	<b>31</b>	<b>12</b>	<b>14</b>	25	79	81
Fakhry (2000) (n=84)	41	EIS	<b>4.8±0.9</b>	15	10	<b>65</b>	20	na	na
	43	EVL	<b>2.8±0.5</b>	16	12	<b>2</b>	21	na	na
*Zargar (2005) (n=73)	36	EIS	<b>7.7±3.3</b>	<b>19</b>	<b>19</b>	<b>22</b>	9	92	na
	37	EVL	<b>3.7±1.2</b>	<b>3</b>	<b>3</b>	<b>3</b>	11	95	na

na = data not available; Comp = complications

\*Extrahepatic portal venous obstruction

Significant differences between EVL and EIS highlighted in **bold type**

**Table 2.7.2 Randomised trials comparing endoscopic band ligation with ligation plus simultaneous sclerotherapy.**

Author (year) (patient numbers)	Patient	Group	Sessions	Re-bleed	Variceal Bleeding	Complications
Laine (1996) (n=41)	20	EVL	<b>2.7(0.4)</b>	30%	25%	10%
	21	EVL/EIS	<b>4.9(0.6)</b>	29%	19%	29%
Saeed (1997) (n=47)	25	EVL	3.3(0.4)	25%	86%	<b>25%</b>
	22	EVL/EIS	4.1(0.6)	36%	63%	<b>65%</b>
Umehara (1999) (n=51)	26	EVL	<b>2.3±0.5</b>	na	Na	46%
	25	EVL/EIS	<b>3.5±1.0</b>	na	na	68%
Al Traif (1999) (n=60)	31	EVL	3.6±0.4	23%	10%	34%
	29	EVL/EIS	3.8±0.5	17%	7%	29%
Djurdjevic (1999) (n=103)	51	EVL	2.3±0.7	14%	10%	2%
	52	EVL/EIS	2.4±0.7	20%	14%	6%
Argonz (2000) (n=80)	41	EVL	3.9±0.3	na	31.7%	7.3%
	39	EVL/EIS	3.8±0.3	na	23.1%	30.8%
Hou (2001) (n=94)	47	EVL	3.7±1.2	23%	Na	na
	47	EVL/EIS	3.8±1.4	28%	na	na

na = data not available

Significant differences between EVL and EIS highlighted in **bold type**

**Table 2.7.3 Randomised trials comparing endoscopic band ligation with ligation plus consecutive sclerotherapy.**

Author (year) (patient numbers)	Patient	Group	Sessions	Re-bleed	Variceal Bleeding	Complications
Bhargava (1996) (n=50)	21	EVL	<b>4.3±1.8</b>	na	19%	31%
	23	EVL/EIS	<b>5.9±2.3</b>	na	22%	44%
Lo (1998) (n=72)	35	EVL	3.7±0.9	<b>31%</b>	5.4%	na
	37	EVL/EIS	3.4±1.1	<b>8%</b>	23%	na
Masumoto (1998) (n=41)	20	EVL	2.3±0.8	0%	0%	<b>5%</b>
	21	EVL/EIS	4.1±0.9	0%	0%	<b>10%</b>

na = data not available

Significant differences between EVL and EIS highlighted in **bold type**

**Table 2.7.4 Randomised trials comparing Injection sclerotherapy with ligation plus sclerotherapy.**

Author (year) (patient numbers)	Patient	Group	Sessions	Re-bleed	Complications	Recurrence	Survival
Iso(1997) (n=61)	30	EIS	4.1 (0.8)	0%	<b>91%</b>	<b>8%</b>	na
	31	EVL/EIS	3.0 (0.5)	4%	<b>22%</b>	<b>39%</b>	na
Masumoto (1998) (n=39)	18	EIS	4.7±1.4	0%	<b>50%</b>	<b>95%</b>	100%
	21	EVL/EIS	4.1±0.9	0%	<b>10%</b>	<b>86%</b>	100%
Nishikawa (1999) (n=28)	14	EIS	<b>3.9±0.8</b>	0%	7%	50%	79%
	14	EVL/EIS	<b>2.3±0.5</b>	0%	14%	45%	64%
Garg (1999) (n=69)	34	EIS	6.6±2.9	<b>16%</b>	<b>20%</b>	85% (5.8%)	91%
	35	EVL/EIS	7.9±3.3	<b>3%</b>	<b>3%</b>	80% (14.2%)	89%
Shigemitsu (2000) (n=24)	12	EIS	2.8±0.6	na	41%	48%	100%
	12	EVL/EIS	2.4±0.7	na	83%	82%	100%

Significant differences between EVL and EIS highlighted in **bold type**

na = data not available

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## **2.7 INJECTION SCLEROTHERAPY TO PREVENT RECURRENT BLEEDING OF OESOPHAGEAL VARICES**

### **2.7.5 Sclerotherapy versus shunt surgery**

Six prospective randomised controlled trials have compared long term injection sclerotherapy with shunt surgery to prevent rebleeding of varices and improve survival in cirrhotic patients with bleeding varices. Two trials compared side to side portocaval shunts with long term endoscopic sclerotherapy and four trials used the Warren selective distal splenorenal shunt.

#### **Portocaval shunt surgery compared to long term endoscopic sclerotherapy**

In a continuation of a trial by the group from San Francisco for which preliminary results were reported in The New England Journal of Medicine two years previously, a total of 64 patients with Child Class C cirrhosis and variceal bleeding requiring six or more units of blood were randomly assigned to receive either a portacaval shunt (32 patients) or endoscopic sclerotherapy (32 patients) (Cello 1987). The duration of initial hospitalisation and the total amount of blood transfused during hospitalisation were significantly less in the patients receiving sclerotherapy ( $p < 0.001$ ). There was no difference in short-term survival (50% of the sclerotherapy group were discharged alive, compared with 44% of the shunt-surgery group). Both groups were followed for a mean of 530 days after randomisation. Rebleeding from varices, the duration of rehospitalisation for bleeding, and transfusions received after discharge were all significantly greater in the sclerotherapy group ( $p < 0.001$ ). Forty percent of the sclerotherapy-treated patients discharged alive (7 of 16 patients) ultimately required surgical treatment for bleeding varices, despite a mean of 6.1 treatment sessions.

Health care costs and long-term survival did not differ significantly between the groups ( $p > 0.05$ ). The authors concluded that although endoscopic sclerotherapy was as good as surgical shunting for the acute management of variceal haemorrhage in poor-risk patients with massive bleeding, sclerotherapy-treated patients in whom varices are not obliterated and bleeding continues should be considered for elective shunt surgery.

In a second study from the Hospital Universitari Germans Trias i Pujol in Barcelona 82 consecutive Child-Pugh grade A and B cirrhotic patients were included in a prospective randomised controlled trial to assess the efficacy and safety of portacaval anastomosis compared to endoscopic sclerotherapy as elective treatment of patients who had bled from oesophageal varices (Planas 1991). Forty-one patients were randomised to a portacaval shunt and 41 to endoscopic sclerotherapy. After excluding dropouts, 34 patients underwent a portacaval shunt and 35 received endoscopic sclerotherapy. The incidence of variceal rebleeding during follow-up (mean  $\pm$  SD, 20.6  $\pm$  14.2 months) was significantly higher in the sclerotherapy than in the portacaval group, considering the overall treated group and only patients completing sclerotherapy (40% and 25% vs 2.9%;  $p = 0.0002$  and  $p = 0.01$ , respectively). The 2-year probability of having at least one episode of hepatic encephalopathy was significantly higher in patients who had a portacaval shunt than in those treated with endoscopic sclerotherapy (40% vs 12%;  $p = 0.04$ ). However, disabling encephalopathy only appeared in 3 of 34 patients who underwent surgery (8.8%). Early and long-term mortality did not differ between the therapeutic groups; 2-year survival rates were 83% for portacaval shunts and 79% for sclerotherapy. Cost, complication rates, days of hospitalization and long-term

mortality were equivalent. The authors concluded that portacaval shunt surgery was more effective than endoscopic sclerotherapy in preventing variceal rebleeding in spite of the greater incidence of hepatic encephalopathy.

### **Distal splenorenal shunt surgery compared to long term endoscopic sclerotherapy**

In a prospective, randomised clinical crossover trial for those failing therapy, Henderson and the Emory Hospital group in Atlanta, Georgia randomised 72 cirrhotic patients drawn from a total of 420 patients treated during a 4.5-year interval to either endoscopic variceal injection sclerotherapy or distal splenorenal shunt to prevent recurrent variceal bleeding (Henderson 1990). Survival was significantly ( $p < 0.02$ ) improved in patients assigned to receive sclerotherapy: 13 of these 37 (35%) patients failed sclerotherapy and required surgical rescue. A survival advantage ( $p < 0.01$ ) was seen in patients with alcoholic cirrhosis who had this combined therapy; however, in patients with nonalcoholic cirrhosis, survival for those receiving sclerotherapy and surgical rescue was not significantly ( $p < 0.36$ ) different from that of patients receiving distal splenorenal shunt. Control of variceal bleeding was significantly ( $p < 0.001$ ) better in the distal splenorenal shunt group (34 of 35 [97%] compared with 15 of 37 [41%] in the sclerotherapy group). Using death, uncontrolled rebleeding, or shunt thrombosis as the endpoints resulted in no significant difference between treatment groups. Hepatocyte function ( $p < 0.01$ ) and portal perfusion ( $p < 0.001$ ) were significantly better maintained in patients with alcoholic cirrhosis who were managed by sclerotherapy rather than shunt. The authors concluded that endoscopic sclerotherapy with surgical rescue for uncontrolled bleeding was the optimum therapy for patients with alcoholic cirrhosis

and variceal bleeding. Survival was similar in nonalcoholic patients treated with either distal splenorenal shunt or endoscopic sclerotherapy, but shunting provided better control of variceal bleeding.

In a prospective controlled trial the group from Barcelona randomised 112 consecutive Child grade A and B cirrhotic patients to either endoscopic injection sclerotherapy or distal splenorenal shunt in order to evaluate the efficacy and safety of each treatment in the elective treatment of haemorrhage from oesophageal varices (Teres 1987). Fifty-seven patients were randomly allocated to splenorenal shunt and 55 to endoscopic sclerotherapy. Four of the 55 patients assigned to endoscopic sclerotherapy were excluded after randomisation and before treatment compared to 14 of 57 patients assigned to splenorenal shunt, suggesting that the applicability of endoscopic sclerotherapy is greater than that of splenorenal shunt. One patient in each group died within 30 days of the procedure and two in the endoscopic sclerotherapy group were lost to follow-up after discharge. Variceal rebleeding during follow-up occurred in 37.5% (18/48) of patients in the endoscopic sclerotherapy group and in 14.3% of those in the splenorenal shunt group (6/42) ( $p < 0.02$ ), while hepatic encephalopathy was more frequent in patients submitted to splenorenal shunt (10/42, 24%) than in those treated by endoscopic sclerotherapy (4/48, 8%) ( $p < 0.05$ ). Early and long term mortality was similar in the two groups; the 2-year survival was 71% in the splenorenal shunt group and 68% in endoscopic sclerotherapy group.

Spina and the group from the San Paolo Institute of Biomedical Science in Milan conducted a prospective controlled trial comparing endoscopic sclerotherapy (EIS) with the distal splenorenal shunt (DSRS) in the elective treatment of variceal

hemorrhage in cirrhotic patients (Spina 1990). The study population included 40 patients with cirrhosis and portal hypertension drawn from a pool of 173 patients. Twenty patients were assigned to DSRS and 20 to EIS. During the postoperative period, no DSRS patient died, while one EIS patient died of uncontrolled bleeding. One DSRS patient had recurrent variceal haemorrhage despite an angiographically patent shunt. Four EIS patients had at least one episode of gastrointestinal bleeding: two from varices and two from oesophageal ulceration. Five EIS patients developed transitory dysphagia. Long-term follow-up was complete. Two-year survival rates for shunt (95%) and EIS (90%) groups were similar. One DSRS patient rebled from a duodenal ulcer, while three EIS patients had recurrent bleeding from oesophagogastric sources (two from varices and one from hypertensive gastropathy). One DSRS and two EIS patients have evolved a mild chronic encephalopathy. Data from this trial indicate that DSRS, in a subgroup of patients with good liver function and a correct portal-azygos disconnection, more effectively prevents variceal rebleeding than EIS. However no significant difference in the survival of the two treatment groups was noted.

A long-term follow-up of these trial patients was completed by Santambrogio and Spina in 2006 except for 5 patients (2 DSRS, 3 EIS patients) (Santambrogio 2006). Five-year survival rates for shunt (73%) and EIS (56%) groups were statistically different. In this follow-up period and in subsequent follow-ups this difference decreased and ceased to be of statistical relevance. The primary cause of death became hepatocellular carcinoma. Four DSRS patients rebled due to duodenal ulcer, while eleven EIS patients had recurrent bleeding from oesophago-gastric sources (seven from varices, three from hypertensive gastropathy, one from

oesophageal ulceration) and two from unknown sources. Nine DSRS and 2 EIS patients developed chronic encephalopathy; 13 DSRS and 5 EIS patients had at least one episode of acute encephalopathy. Five EIS patients had oesophageal stenoses, which were successfully dilated. The authors concluded that in a subgroup of patients with good liver function, DSRS with a correct portal-azygos disconnection more effectively prevents variceal rebleeding than EIS. However, this positive effect did not influence the long-term survival because other factors such as hepatocellular carcinoma were more important in deciding the fate of cirrhotic patients with portal hypertension.

Rikkers and the group from the University of Nebraska Medical Center in Omaha, Nebraska, randomised 60 cirrhotic patients with prior variceal haemorrhage to either an elective shunt (distal splenorenal: 26; nonselective: 4) or long term endoscopic sclerotherapy (n = 30). Eighty-six percent of the patients had alcoholic cirrhosis, and 33% were classified as Child's grade C (Rikkers 1993). After a mean follow-up of 87 months, 60% of patients undergoing sclerotherapy and 17% of shunt patients experienced rebleeding ( $p < 0.001$ ). Shunt patients survived longer than those who had sclerotherapy (6-year survival rates of 53% and 26%, respectively;  $p < 0.05$ ). In part because of the wide geographic distribution of patients, only 4 of 13 patients in whom sclerotherapy failed (31%) could undergo salvage by shunt surgery. Posttherapy quantitative hepatic function, frequency of encephalopathy, and cumulative medical costs were similar for both groups. Hepatic portal perfusion and portal pressure at 1 year were better maintained by sclerotherapy than by distal splenorenal shunt. The authors concluded that endoscopic sclerotherapy and shunt surgery provided similar results with respect to survival, hepatic function, frequency

of encephalopathy, and costs and that sclerotherapy was an acceptable, but not superior, alternative to shunt surgery for treatment of variceal haemorrhage.

In a meta-analysis of these data, Spina et al evaluated the 4 clinical trials which compared distal splenorenal shunt (DSRS) with endoscopic sclerotherapy (EIS) in the prevention of variceal rebleeding (Spina 1992). A questionnaire was sent to each author of the published trials to clarify the methods, definitions and results of the trials in order to obtain more detailed information. The selected end-points for the meta-analysis were rebleeding, mortality and chronic encephalopathy. The pooled relative risk (i.e. the combined odds ratio of each trial as an estimate of overall efficacy) of rebleeding was statistically reduced by DSRS (0.16; 95% confidence interval 0.10-0.27). Despite this, the overall risk of death following DSRS was only marginally decreased (0.78; 95% confidence interval 0.47-1.29); the lack of homogeneity in the results did not permit any significant conclusions on this end-point. However, in non-alcoholic patients, the decrease in risk of death was greater, and this without heterogeneity, following DSRS than EIS (0.59; 95% confidence interval 0.23-1.50). The overall risk of chronic encephalopathy was slightly increased after DSRS (1.86; 95% confidence interval 0.90-3.86). In conclusion, DSRS significantly reduced the risk of rebleeding compared to EIS without increasing the risk of chronic hepatic encephalopathy. However, DSRS did not significantly affect the overall death risk. Only in non-alcoholic disease did it seem to show an advantage over EIS.

The results of elective shunt surgery were superior to those of chronic endoscopic sclerotherapy with respect to the prevention of recurrent variceal haemorrhage and

recurrent bleeding was significantly less frequent after the distal splenorenal shunt in all studies. Only one study found a significant difference between therapies with regard to survival (Henderson 1990). In that trial, approximately one-third of the patients in the sclerotherapy group were successfully salvaged by surgery when they failed to improve with sclerotherapy, thus resulting in a survival advantage to this treatment. In contrast to the Atlanta study in which nearly all of the sclerotherapy failures could be salvaged by shunt surgery, the majority of sclerotherapy failures in the Omaha, Nebraska trial (Rikkens 1987) died of hepatic failure before they could undergo surgery. The reason for the lower salvage rate of sclerotherapy failures in the latter trial was the inclusion of patients from a wider geographic area. Many of the sclerotherapy failures in this trial died in peripheral hospitals or were not salvageable by the time they were referred for alternative treatment. Two of the randomized studies (Rikkens 1987, Henderson 1990) showed no difference in postoperative encephalopathy after distal splenorenal shunt and endoscopic sclerotherapy, while the third investigation (Teres 1987) demonstrated a higher encephalopathy rate in the shunt group. Two of the trials (Rikkens 1987, Henderson 1990) evaluated the effect of these interventions on postoperative hepatic portal perfusion and quantitative tests of liver function. Significantly more patients had continuing portal flow to the liver at the 1 year assessment in the sclerotherapy groups of both these trials. This haemodynamic advantage resulted in superior hepatic functional reserve in one trial (Henderson 1990), but not in the other (Rikkens 1987).

An objective assessment of the results of all three of these studies suggests that long term sclerotherapy is a reasonable initial treatment for many patients who bleed

from oesophageal varices. However, approximately one-third of the patients in these studies eventually failed sclerotherapy and required operative intervention for control of recurrent variceal bleeding. Rikkers concluded that patients who live in remote geographic areas or patients who are non-compliant and unwilling to return for repeated sclerotherapy sessions should undergo an initial selective shunt rather than long term sclerotherapy (Rikkers 1987). In all the trials, days in the hospital after the index bleeding episode were significantly fewer in patients undergoing sclerotherapy, but on a long-term basis, days in the hospital were equal because of the higher rates of recurrent bleeding and complications in the sclerotherapy group. Teres concluded that the applicability of sclerotherapy was wider based on the numbers of patients excluded from both treatment arms of the trial (Teres 1987).

In a systematic review by a Cochrane hepatobiliary group from Birmingham, all prospective randomised clinical trials which have compared portosystemic shunting procedures with endoscopic therapy for variceal bleeding were evaluated (Kahn 2006). The search strategy included the Cochrane Hepato-Biliary Group Controlled Trials Register, the Cochrane Library, Medline, Embase, conference proceedings, and the references of identified trials were searched. Data were collected to allow intention-to-treat analysis where possible. For each outcome, a pooled estimate of treatment effect (log hazard ratio for time to outcome, Peto odds ratio for binary outcomes, and differences in means for continuous outcomes) across trials was calculated. Shunt therapy compared with EIS demonstrated significantly less rebleeding (OR 0.24, 95% CI 0.18 to 0.30) at the cost of significantly increased acute hepatic encephalopathy (OR 2.07, 95% CI 1.59 to 2.69) and chronic encephalopathy (OR 2.09, 95% CI 1.20 to 3.62). There were no significant differences regarding

mortality (hazard ratio 1.00, 95% CI 0.82 to 1.21) and duration of in-patient stay (weighed mean difference 0.78 day, 95% CI -1.48 to 3.05). The proportion of patients with shunt occlusion or dysfunction was 7.8% (95% CI 3.8 to 13.9%) following DSRS. The authors concluded that DSRS resulted in a significantly lower rebleeding rate at the expense of a higher incidence of encephalopathy. No survival advantage was demonstrated.

University of Cape Town

## **2.7 INJECTION SCLEROTHERAPY TO PREVENT RECURRENT BLEEDING OF OESOPHAGEAL VARICES**

### **2.7.6 Sclerotherapy versus transjugular intrahepatic shunt**

The introduction of minimally invasive, radiologically placed transjugular intrahepatic portosystemic shunts (TIPS) has provided a valuable addition to the treatment options in the management of patients with portal hypertensive bleeding due to decompensated cirrhosis (Rosado 2003, Boyer 2005). The most common indication for TIPS is uncontrolled or refractory variceal bleeding unresponsive to standard pharmacological and endoscopic therapy (Rosado 2003, Boyer 2005). TIPS placement by a skilled interventional radiologists has a mortality rate of less than 1%. Life-threatening, procedure-related complications include intraperitoneal haemorrhage from puncture of the liver capsule, sepsis, haemobilia due to portobiliary fistulae, worsening hepatic failure, and cardiopulmonary failure (Luca 1999, Papatheodoridis 1999, Burroughs 2002, Khan 2006, Zheng 2008).

The major disadvantages after TIPS are hepatic encephalopathy and stent dysfunction. Hepatic encephalopathy after TIPS placement usually occurs within the first month of the procedure and is more likely in patients with advanced liver disease but usually responds to standard treatment including lactulose, protein restriction and elimination of precipitating factors. A minority of patients may develop intractable encephalopathy requiring shunt modification either by mechanical reduction of the shunt diameter or by total occlusion of the shunt. Ultimately liver transplantation is the treatment of choice for refractory hepatic encephalopathy (Rosado 2003, Boyer 2005).

Shunt dysfunction due to stenosis or occlusion remains a major limiting factor in the long-term success of TIPS. Shunt stenosis is the result of pseudointimal hyperplasia which causes focal narrowing of the lumen of the shunt at the hepatic venous end of the TIPS or diffusely within the parenchymal tract. Since TIPS stenosis is the most important cause of recurrent portal hypertension and variceal bleeding after TIPS placement, a surveillance program to monitor shunt patency is mandatory. The best strategy for TIPS surveillance has yet to be defined (Rosado 2003, Boyer 2005).

### **Endoscopic injection sclerotherapy compared to TIPS**

Eight randomised controlled trials have compared endoscopic injection sclerotherapy with TIPS in the prevention of recurrent oesophageal variceal bleeding.

In a Spanish trial, 63 patients were randomised within 3 days of the onset of variceal bleeding to either TIPS (n = 31) or sclerotherapy (n = 32) (Cabrera 1996). There was a significant difference in the rate of recurrent variceal bleeding in favour of TIPS (23% vs 51.6%) at a mean follow-up of 15 months. In 10 patients in the sclerotherapy group, recurrent bleeding was uncontrollable and 8 of these patients underwent TIPS. One third of patients who underwent TIPS developed encephalopathy or in some patients encephalopathy worsened, compared to 13% of those who had sclerotherapy. There was no significant difference in survival between the two groups.

In a study from the University of California at San Francisco, 49 patients were randomised to either TIPS (n=24) or sclerotherapy (n=25) within 24 hours of the onset of variceal bleeding (Cello 1997). At mean follow up periods of 575 and 567

days, the frequency of recurrent bleeding was significantly less for patients who underwent TIPS (12.5 % vs 48%). Six patients (24%) in the sclerotherapy group underwent TIPS for recurrent variceal bleeding. Although a trend toward improved survival for TIPS treated patients was noted, the difference was not statistically significant. In this trial, there were no significant differences in the new onset or worsening of encephalopathy that existed before randomisation and there were no significant differences between the two groups for total days of hospitalisation for variceal bleeding and total health care costs.

In the German trial from the University of Freiburg, 61 patients were randomised to undergo TIPS and 65 to have sclerotherapy or band ligation, or both, combined with propranolol therapy within 24 hours of the onset of bleeding (Rossle 1997). Episodes of bleeding had occurred before randomisation in 61% of patients in the study. The cumulative 1 year and 2 year recurrent bleeding rates were significantly less in the TIPS group compared with sclerotherapy (15% vs 41%, and 21% vs 52%). At 1 year the rate of clinically significant encephalopathy was considerably higher in the TIPS group (35% vs 18%), but there was no significant difference in mortality between the two groups.

Forty one patients were randomised to TIPS and 39 to sclerotherapy in an American trial by Sanyal and colleagues after an episode of variceal bleeding (Sanyal 1997). At 3 years, the rates of recurrent variceal bleeding after TIPS or sclerotherapy were similar (22% vs 20.5%). Six patients (15%) in the sclerotherapy group underwent TIPS for recurrent bleeding. Encephalopathy developed in 29.3% of patients who underwent TIPS. The mortality rate was significantly higher in the TIPS group. In

contrast to the studies by Cabrera et al. and Rossle et al. in which there were no deaths as a result of variceal bleeding in the TIPS treatment group, in this study 5 patients in the TIPS group and 3 who underwent sclerotherapy died as a result of bleeding.

In the German study from the University of Heidelberg, Sauer and colleagues compared TIPS and endoscopic sclerotherapy plus propranolol in cirrhotic patients after a first variceal bleed (Sauer 1997). Eighty-three patients were randomised to either TIPS (n = 42) or EVS (n = 41). Median observation time was 1.6 years in the TIPS group and 1.45 years in the EVS group. Cumulative rates of rebleeding were 23% in the TIPS group and 57% in the EVS group ( $p < 0.0001$ ). Hepatic encephalopathy occurred in 29% of the TIPS patients and in 13% of the EVS group ( $p < 0.041$ ). Cumulative rates of survival were 69% in the TIPS group and 67% in the EVS group ( $p = 0.62$ ). Mortality rates in both groups were positively correlated with a higher Child's grade. The authors concluded that although TIPS significantly reduced the rate of rebleeding, survival rates were not improved. Because TIPS was associated with an increased risk of encephalopathy and high rates of shunt dysfunction, which required reintervention, TIPS could not be recommended for elective treatment after the first variceal bleeding episode, but was an effective therapy in patients in whom endoscopic sclerotherapy failed to control bleeding.

In a multicentre randomised controlled trial from Rome, the efficacy of TIPS was compared to endoscopic sclerotherapy in the prevention of variceal rebleeding (Merli 1998). Eighty-one patients were randomised to either TIPS (38 patients) or endoscopic sclerotherapy (43 patients). Randomisation was stratified according to

the following criteria: if bleeding had occurred < 1 week (stratum I); if bleeding had occurred 1 to 6 weeks (stratum II); and if bleeding had occurred 6 weeks to 6 months (stratum III) before enrollment. Follow-up included clinical, biochemical, Doppler ultrasound and endoscopic examinations every 6 months. During a mean follow-up of 17.7 months, 51% of the patients treated with sclerotherapy and 24% of those treated with TIPS rebled ( $p < 0.011$ ). Mortality was 19% in sclerotherapy patients and 24% in TIPS patients ( $p = 0.50$ ). Hepatic encephalopathy developed in 26% and 55% ( $p < 0.006$ ). A separate analysis of the three strata showed that TIPS was significantly more effective than sclerotherapy ( $p < 0.026$ ) in preventing rebleeding only in stratum I patients. TIPS was significantly better than sclerotherapy in preventing rebleeding only when performed shortly after a variceal bleed; however, TIPS did not improve survival and was associated with a significantly higher incidence of hepatic encephalopathy. The overall performance of TIPS did not justify its use as the first-choice treatment to prevent rebleeding from oesophageal varices in cirrhotic patients.

In a study from Spain, 46 cirrhotic patients with variceal bleeding were randomly allocated to receive either TIPS (22 patients) or EVS (24 patients) 24 hours after control of bleeding (Garcia-Villarreal 1999). Overall variceal bleeding (50% vs 9%) and early variceal bleeding during the first 6 weeks (33% vs 5%) were significantly more frequent in sclerotherapy patients. The actuarial probability of being free of variceal bleeding was higher in the shunt group ( $p < 0.002$ ). Eight patients (33%) in the sclerotherapy group and 3 patients (15%) in the shunt group died; the actuarial probability of survival was higher for the shunted patients ( $p < 0.05$ ); 6 patients in the sclerotherapy group and none in the shunt group died of variceal bleeding ( $p < 0.05$ ).

No difference was found in the proportion of patients with clinically evident hepatic encephalopathy. These results showed that TIPS was more effective than sclerotherapy in the prevention of both early and long-term variceal bleeding. Moreover, a significant improvement in survival was found in the shunt group.

In a study from Tokyo the efficacy of TIPS was compared with endoscopic sclerotherapy in the long-term management of patients with cirrhosis after variceal bleeding (Narahara 2001). Seventy-eight cirrhotic patients with recent variceal bleeding were randomly allocated to either TIPS (n=38) or EVS (n=40). Mean follow-up was 1116 +/- 92 days in the TIPS group and 1047 +/- 102 days in the EVS group. Differences in rebleeding from any source (18.4% vs 32.5%) and oesophageal variceal rebleeding (15.7% vs 27.5%) were not significantly different between the two groups ( $p>0.05$ ). The mortality rates were similar in both treatment groups. Shunt dysfunction was noted in 27 patients (71%) in the TIPS group. There were more numbers of rehospitalisation during follow-up in the TIPS group than in the EVS group (2.6 +/- 0.4 vs 1.1 +/- 0.2) ( $p<0.01$ ). TIPS and EVS were equally effective in the prevention of variceal rebleeding. However, TIPS was associated with high incidence of shunt dysfunction which led to more rehospitalisation. The authors recommended that TIPS should not be used as first-line treatment for the prevention of variceal rebleeding in cirrhotic patients who were stable.

The results of these eight randomised controlled trials and subsequent 5 meta-analyses have shown that TIPS is superior to endoscopic and pharmacological therapy in preventing variceal rebleeding (Luca 1999, Papatheodoridis 1999, Burroughs 2002, Khan 2006, Zheng 2008). Although there is a reduction in

rebleeding rates, TIPS is associated with a significantly increased risk of hepatic encephalopathy and long-term shunt dysfunction. In these trials TIPS resulted in a significantly higher incidence of new or worsened encephalopathy, as well as a significantly higher incidence of chronic encephalopathy. New-onset encephalopathy or evidence of worsening encephalopathy was observed in one third of patients undergoing TIPS compared to 15% of patients treated by sclerotherapy. The difference between the two treatment groups with regard to encephalopathy was significant in all studies. In all instances, however, this was reported to be treatable and did not lead to disabling encephalopathy (Luca 1999, Papatheodoridis 1999, Burroughs 2002, Khan 2006, Zheng 2008).

A further important complication in the TIPS group was shunt insufficiency or dysfunction as well as shunt occlusion, as a result of thrombosis. Shunt dysfunction is a major problem that leads to a higher rate of re-intervention, recurrence of complications associated with portal hypertension (variceal rebleeding, ascites), and increased costs. Such TIPS failure was the commonest cause of rebleeding in this group. As the follow-up period of most trials was short (< 2 years), one would expect that the rate of rebleeding would increase over time in the TIPS group. Therefore, vigorous surveillance is necessary for the early recognition and treatment of TIPS dysfunction. No consensus exists in the criteria used to define either TIPS dysfunction or the frequency, and interval for surveillance. The long-term results of studies using coated stents to prevent shunt dysfunction are awaited. Future investigations exploring issues such as cost effectiveness and quality of life, as primary end points are also needed (Luca 1999, Papatheodoridis 1999, Burroughs 2002, Khan 2006, Zheng 2008).

In the detailed analysis of the data there are similarities, differences and deficiencies in the results of these 8 trials. The treatment provided, including TIPS and sclerotherapy, were not strictly comparable because of differences in the level of operator skill and experience, techniques used and the additional use of other treatments such as variceal banding and prophylactic pharmacotherapy. In these trials 32 to 61% of patients had survived prior episodes of bleeding and had been treated by endoscopic means. In some studies, therefore, each treatment group was composed of selected patients for whom the natural history of variceal bleeding was likely to be different from that for a group of patients with new-onset variceal bleeding. In all these studies, recurrent bleeding was the primary endpoint and all except two demonstrated a significantly higher rebleeding rate in patients who underwent sclerotherapy, probably due to a selection bias as a result of a long lead time between randomisation and treatment and failure to adequately reduce portal pressure in some patients in the TIPS group. Furthermore, there was no improvement in overall survival with TIPS compared to endoscopic or medical therapy (Luca 1999, Papatheodoridis 1999, Burroughs 2002, Khan 2006, Zheng 2008).

In addition, these trials have shown considerable variation in quality with regard to generation of allocation sequence and allocation concealment which raises the risk of selection bias (Schulz 1995, Kjaergard 2001). None of the trials performed blinded the outcome assessment which also raises the risk of assessment bias. Furthermore, a number of trials had unclear reporting of follow-up, which may introduce attrition bias. The lack of statistical power of several trials is a major deficiency in this field, where modest survival advantages are unlikely to be detected

unless large-scale, multicentre randomised trials are undertaken (Schulz 1995, Kjaergard 2001). Further issues have been highlighted at the Baveno Consensus Conferences (de Franchis 1992, Franchis 1996, de Franchis 2001, de Franchis 2005), including appropriate randomisation and blinding, as well as the need for accurate data on all evaluable patients, trial events, and costs. In particular the need for accurate data on the timing and assessment of all individual components of Child-Pugh grading should be emphasised, especially for encephalopathy (Luca 1999, Papatheodoridis 1999, Burroughs 2002, Khan 2006, Zheng 2008).

The implications of these studies for clinical practice are that endoscopic therapy should be the first-line treatment in the prevention of variceal rebleeding but in centres with expertise and experience in shunting procedures the latter options should carefully be discussed with the patient. When recurrent rebleeding occurs after endoscopic therapy, selected shunting procedures should be offered at an early stage to those who are fit to undergo these procedures.

## **2.8 COMPLICATIONS OF ENDOSCOPIC VARICEAL INJECTION SCLEROTHERAPY**

### **2.8.1 Incidence**

### **2.8.2 Oesophageal complications**

#### **2.8.2 Morphologic changes**

2.8.2.1 Ulceration

2.8.2.2 Bleeding

2.8.2.3 Perforation

2.8.2.4 Intramural haematoma

2.8.2.5 Stricture

2.8.2.6 Motility disorders

2.8.2.7 Other oesophageal complications

Endoscopic variceal sclerotherapy has been widely used as a method of treatment for control of acute variceal haemorrhage, and repeated injections have been shown to reduce the frequency of subsequent episodes of bleeding (Terblanche 1983, Terblanche 1985, Terblanche 1989, Krige 2000b). Although variceal sclerotherapy has used as one of the principal endoscopic treatment options for variceal bleeding, the procedure is not without risk. More than 40 different complications which have occurred as a consequence of endoscopic variceal injection sclerotherapy, have been described (Sanowski 1987, Schuman 1987, Kahn 1989, Baillie 1992, Muhldorfer 1992, Krige 2005). Important factors influencing the complication rate are the experience of the endoscopist, the injection technique used, the use of ancilliary devices including balloon tamponade, and whether sclerotherapy is performed as an emergency or elective procedure. Other interrelated anatomic factors are the close proximity of the oesophagus to vital mediastinal structures, repetitive breaching of the oesophageal mucosa by the injecting needle, and the potential for pulmonary and systemic dissemination of sclerosant through portal venous collaterals (Baillie 1992, Schuman 1985).

## **Incidence**

There is no consensus regarding the definition or classification of the complications that occur after endoscopic variceal sclerotherapy, and consequently the incidence varies widely in reported studies (Krige 1999b). Much of the published data are flawed because the reporting process often is biased with subjective and retrospective information, short or incomplete follow-up and naïve statistical analysis. Complication rates are generally operator dependent (Baillie 1994) and comparative analyses of complication rates in many series are hampered by variations in patient population, type and severity of the underlying liver disease and the sclerotherapy technique used (Krige 2000). In addition, differences in study design introduce a covert selection bias which may influence results. These biases include sampling and selection bias (specialist centres, expert endoscopists, different patient populations) confounding bias (emergency versus elective procedures) and measurement bias (incomplete reporting, delayed complications).

In addition, many patients undergoing endoscopic variceal intervention have a limited prognosis and therefore complications may not be identified or treated aggressively. The debilitated state of many patients undergoing endoscopic therapy contributes to the medical difficulties encountered, often making the differentiation of a true complication of the procedure difficult (Chan 1996). Complication rates are also higher when carefully documented in prospective studies (Krige 2000). Some studies express complication rates in terms of incidence per patient treated while others describe complication rates in terms of incidence per procedure performed. Surprisingly, in some prospective studies, details of sclerotherapy complications are omitted, while other studies only consider major events. In long-term studies,

repeated injections also increase the cumulative risk of sclerotherapy-induced complications in the individual patient (Krige 2000a). The most reliable data indicate that 10% to 15% of patients undergoing variceal sclerotherapy will develop a major complication (Krige 2005) but less than 1% of patients die as a direct result of the procedure.

### **Classification of sclerotherapy complications**

In this dissertation endoscopic sclerotherapy-induced complications have been categorised as (i) local effects involving the oesophagus, including ulceration, stricture and perforation; (ii) regional respiratory and cardiovascular effects; and (iii) distant or systemic consequences (Krige 1999b). Minor events have been defined as those that are self-limiting and do not require specific treatment and do not interfere with the regular sclerotherapy injection programme. Major complications are serious or life-threatening events that require or prolong hospitalisation (Krige 1999b).

### **Oesophageal complications**

#### **Morphological changes**

Oesophageal complications of endoscopic variceal sclerotherapy are invariably a consequence of excessive sclerosant-induced submucosal or transmural oesophageal necrosis (Krige 1999b). The few studies that have examined the local histopathological effects of sclerosant on the oesophageal wall in detail have been based on necropsy studies. Although the injection techniques, type and volume of sclerosant used, and intervals between injections vary in these studies, the histopathological findings are remarkably similar and provide a time-dependent

morphological profile of the effects of variceal sclerotherapy on the oesophagus (Helpap 1981, Evans 1982, Papadimos 1986, Pushpanathan 1986)

The earliest changes in the oesophageal wall during the initial 48 hours after variceal injection of sclerosant are thrombosis in the superficial veins, submucosal oedema, and minor areas of tissue necrosis (Helpap 1981). Mucosal ulceration is uncommon during this phase and no significant cellular reaction occurs (Kage 1987). After 48 hours, progressive tissue necrosis occurs, predominantly in the superficial layers and to a lesser extent in the deeper tissues. During the first week, mucosal ulceration and a marked acute polymorphonuclear leucocyte inflammatory response occurs which is followed by an intense macrophage and fibroblast infiltration (Helpap 1981, Ayres 1983). Intramural microabscesses may develop as a consequence of localised necrotising inflammation. In some cases, extravasation of sclerosant into the submucosa and muscle layers results in a giant cell reaction and focal calcification. Some residual varices remain patent, but others contain thrombi in the early stages of endothelial and fibroblastic organisation (Papadimos 1986, Soehendra 1983).

The extent of sclerotherapy-induced ulceration varies from small, linear, superficial defects to extensive, wide-based ulcers (Papadimos 1986). Although most ulcers are limited to the submucosa or inner layer of the muscularis propria, a few extend more deeply into the muscularis propria. A fourth of necropsy specimens show transmural necrosis which may progress to mediastinitis (Papadimos 1986).

The chronic reaction is characterised by an evolution from granulation tissue to mature collagen, with an accompanying chronic inflammatory cell infiltrate that becomes less prominent with time (Ayres 1983). Necrosis and ulceration may persist for as long as 3 weeks. Organised thrombi and fibrosis become evident 1 month after the injection of sclerosant (Evans 1982, Papadimos 1986). Fibrosis is usually limited to the submucosa and the inner muscularis propria but may occur as a localised transmural breach in muscle or as diffuse transmural fibrosis encasing residual varices (Ayres 1983). Marked thickening of the oesophageal wall is present in seen in some specimens (Kage 1987)

### **Ulceration**

Small areas of superficial mucosal ulceration are a common finding in the lower oesophagus after variceal sclerotherapy (Sarles 1985, Larson 1986, Terabayashi 1987, Low 1989). Some investigators have considered ulceration as an inevitable and necessary consequence of effective sclerotherapy (Sarin 1986, Kitano 1987). The reported incidence ranges from 9% - 87% (Krige 2005). In a detailed prospective study performed in Cape Town, the incidence was 41% on a per-patient basis and 19% on a per-procedure basis (Krige 2005).

The prevalence and extent of ulceration is reported to depend on the type (Kitano 1989, Kitano 1988) and volume (Neeman 1991, Iso 1988) of sclerosant injected, the method of variceal injection (Sarin 1987), the interval between injections (Westaby 1984, Sarin 1986, Higashi 1989) and the size of varices (Choudhuri 1989). Robertson et al, in a study using rabbit stomachs, found that 5% ethanolamine oleate was the least ulcerogenic agent when compared to 2% or 3% sodium

tetradecyl sulphate, 2% or 3% polidoconal and 5% sodium morrhuate (Robertson 1989). In a clinical study, 2% sodium tetradecyl sulphate caused significantly more ulceration than 5% ethanolamine oleate when a combined paravariceal and intravariceal injection technique was used (Kitano 1988). Ulceration is reported to occur more frequently with Child's class C liver disease and after injection of large varices (Choudhuri 1989).

There is evidence that increasing volumes of sclerosant may be implicated in the occurrence of deep ulceration. Madonia et al evaluated forty patients endoscopically 1 week after sclerotherapy with 1% sodium tetradecyl sulphate (Madonia 1990). Those who developed deep ulcers had received significantly greater total volumes of sodium tetradecyl sulphate (12.8 ml compared with 9.3 ml) than those with shallow ulceration. The incidence of deep ulceration was also increased with the associated use of balloon tamponade. Singal et al in a clinical study using absolute alcohol, found that the incidence and size of the ulcers was directly related to the volume injected (Singal 1990). In a canine model with oesophageal varices, Sugawa et al demonstrated that increasing volumes of 5% sodium morrhuate injected intravariceally caused greater necrosis and ulceration (Sugawa 1978).

In a randomised study comparing techniques, Sarin et al found no significant difference in the incidence of ulceration between paravariceal and intravariceal injections using 50% ethanol (Sarin 1987). The risk of ulceration may be related more to the intensity of the sclerotherapy programme than to the technique of injection (Sarin 1987, Westaby 1984, Sorensen 1984). However, it is not always

possible, even in controlled studies, to determine the individual ulcerogenic potential of various sclerosants or the factors primarily responsible for oesophageal ulceration.

Superficial ulceration is not necessarily harmful, and has been deliberately produced as part of the injection technique proposed by Kitano et al to enhance eradication of varices (Kitano 1987). As described by Kitano, the initial and second injection one week later are given intravariceally using a transparent overtube over the flexible endoscope. After variceal thrombosis has occurred, subsequent injections are placed submucosally to create a circumferential ulcer involving the lower 5 to 10 cm of the oesophagus. In their study, healing by epithelialisation occurred, and although pain, pyrexia and pleural effusions were common, no serious complications were encountered. Varices were eradicated in all survivors without any variceal recurrence. An important consideration not reported by the authors is the long term incidence of oesophageal strictures after this procedure (Kitano 1987).

In most instances, minor areas of superficial ulceration are asymptomatic and usually heal rapidly without the need for specific treatment. Singal et al evaluated the symptoms associated with ulceration after 0.5-2ml intravariceal injections of absolute alcohol (Singal 1990). All 40 patients in their study had mucosal ulceration when examined endoscopically soon after sclerotherapy but only two thirds were symptomatic, with mild dysphagia (53%), mild to moderate retrosternal pain (28%) and low-grade fever (15%). Patients with large ulcers (>1cm in diameter) were more likely to be symptomatic. The dysphagia and chest pain usually improved rapidly and resolved within days, even though ulcer healing took longer.

To prevent sclerotherapy-induced ulcers and their complications, sucralfate, H<sub>2</sub>-receptor blocking agents, and antacids, alone or in combination, have been used (Tamura 1991, Pacquet 1991, Roark 1984, Polson 1989). Although sucralfate may reduce recurrent bleeding from ulceration, the frequency and extent of ulcers are similar in patients who had not received sucralfate (Polson 1989). Another controlled trial suggested that ulcer healing may be accelerated by sucralfate, especially in patients with deep ulceration (Pacquet 1991). The ulcers healed more slowly in patients with a serum albumin level of less than 3 g/dl (Singal 1990). In the study of Kumar et al., 31 patients were randomised to receive sclerotherapy plus ranitidine (300 mg per day) or sclerotherapy alone. Varices were treated until eradication, and the treatment groups were said to be similar with respect to the mean number of treatment sessions, time and volume of sclerosant required for eradication. Significant reductions in the frequency of sclerotherapy-associated oesophageal ulceration and episodes of recurrent bleeding were observed in the group that took ranitidine (Kumar 1993).

A small proportion of ulcers persist, despite prolonged treatment with high-dose H<sub>2</sub>-receptor antagonists and sucralfate. In a small group of patients with complicated chronic ulcers, Gimson et al achieved complete healing in all patients after an 8-week course of 40 mg of omeprazole daily (Gimson 1990). Similar results for a small number of patients were reported by Johlin et al (Johlin 1992). The rapid healing of resistant ulcers with omeprazole suggests that such ulcers are perpetuated by mucosal damage from continuing gastroesophageal reflux. The investigators suggest that consideration should be given to even earlier use of omeprazole for postsclerotherapy ulcers complicated by symptoms or bleeding.

Further studies are needed to determine the role of medical therapy for both the prevention and treatment of variceal sclerotherapy-induced ulceration.

### **Bleeding**

Bleeding from the needle puncture site during variceal sclerotherapy is common and can usually be controlled without difficulty by an adjacent small volume submucosal injection or by tamponade using the side of the flexed tip of the endoscope. More severe bleeding may result from variceal laceration or accidental entry of the hilt and needle sheath into the varix in a restless or heaving patient. This can be avoided by retracting the needle into the sheath between injections (Krige 2007). Early recurrent bleeding is the most common major life-threatening event after sclerotherapy and occurs in 18 to 55% of patients (Krige 2009b). Urgent endoscopy is important to establish whether recurrent bleeding is from a varix, or from sclerosant-induced ulceration, or oesophagitis or another source. If the recurrent bleeding is variceal in origin, further sclerotherapy to control the bleeding is indicated. Although control of acute variceal bleeding is usually achieved with a single injection session in 70% of patients, some patients require further injections (Kahn 1989). There is evidence to suggest that somatostatin may be helpful in this situation (Jenkins 1992). If variceal bleeding recurs despite two adequate injections, mortality increases exponentially, and some other definitive procedure should be employed (Bornman 1986, Burroughs 1989).

Bleeding from ulceration after variceal sclerotherapy may be particularly troublesome and occurs in as many as 13.3% of patients (Schuman 1987, Sauerbruch 1985, Palani 1981). It may be difficult to exclude a variceal component aggravating the

haemorrhage because of the complex venous anatomy of the lower oesophagus (Kitano 1986). Repeat sclerotherapy is inappropriate in patients with deep ulceration or oesophagitis, and may aggravate or compound the problem. Bleeding in most ulcers is self-limited or stops with the addition of vasopressin and sucralfate (Kahn 1989, Roark 1984). The small group that continue to bleed pose a major management problem. Balloon tamponade increases the risk of pressure necrosis and perforation. Oesophageal transection may be hazardous after previous injection sclerotherapy, and shunt surgery may be inappropriate in cirrhotic patients with poor liver function (Durtschi 1986). In this difficult situation, the Jenkins et al were able to control severe bleeding in 20 of 22 patients using intravenous somatostatin (250 ug/h) (Jenkins 1991).

## **Perforation**

### *Contained Perforation*

Deep ulceration with transmural necrosis may progress to a localised or contained perforation without mediastinitis or communication with the pleural cavity (Kahn 1989, Shemesh 1986). Such confined perforations should be suspected in patients who have persistent pain and pyrexia after variceal sclerotherapy, and the diagnosis is confirmed on gastrografen swallow. Kahn et al recorded this complication in 25 (8.2%) of 304 patients (Kahn 1989). These patients were treated with antibiotics, parenteral hyperalimentation, or enteral feeding via a fine-bore Silastic nasoduodenal tube. In most patients, subsequent sclerotherapy was delayed for 3 to 4 months. Seven of the 25 patients died; two after a devascularization operation for continued bleeding from the ulceration, and five died of progressive liver failure. The remaining 18 patients recovered after conservative treatment (Kahn 1989).

### *Free Perforation*

Free perforation occurs in 2% - 5% of patients and has a prohibitive mortality rate, especially in patients with advanced liver disease. Perforation was more frequent when the rigid oesophagoscope was used for sclerotherapy and was due to instrumental injury (Borman 1988, Kahn 1989, Terblanche 1989). Perforation after fibre-optic injection sclerotherapy is usually delayed and is the result of deep ulceration and transmural necrosis (McGrew 1985). The risk of perforation is greatest in patients requiring repeated injections for uncontrolled or recurrent bleeding during the index admission (Pillay 1990, Bacon 1987). During these sessions, large cumulative volumes of sclerosant are often used, and the risk of inadvertant misplaced, deep injections is greatest (Grobe 1984, Soderlund 1983). Possible aggravating factors that could predispose the patient to delayed perforation include concurrent balloon tamponade, impairment of healing secondary to poor liver function, mucosal ischaemia associated with infusion of vasopressin, prolonged nasogastric intubation and colonization of the ulcer base with *Candida albicans* (Soderlund 1983, Barthel 1987).

Free perforation generally occurs 10 to 14 days after the index injection session (Goldberg 1995). Analysis of patients for whom detailed clinical information is available reveals a prodrome with several features in common (McGrew 1985, Bacon 1987, Vickers 1989, Huizinga 1984, Shibuya 1989, Perino 1987). Most patients developed deep local ulceration at the injection site following urgent or emergency sclerotherapy during their index admission. Most patients had severe, prolonged retrosternal and pleuritic chest pain, fever, an exudative pleural effusion

and worsening encephalopathy. The effusions were initially sterile, but invariably became infected with a variety of organisms (Goldberg 1995). Gram-negative septicaemia, shock, and deteriorating liver function with multiple organ failure was a common outcome despite adequate surgical or tube drainage. Some patients may not manifest the clinical features of an oesophageal leak but present only with subtle signs of sepsis, worsening encephalopathy or deteriorating liver function, with the diagnosis frequently being made at necropsy (Bacon 1987, Korula 1989).

Free oesophageal perforation poses a major management problem. Oesophageal necrosis, mediastinal venous collaterals, and sepsis with multiple organ failure preclude conventional treatment for oesophageal perforation. At thoracotomy, the tissues are friable and oedematous, making repair difficult and likely to break down. Most reported perforations were managed conservatively with tube thoracostomy, and the mortality rate was high for patients who had this complication. This reflects the reluctance to institute major operative treatment for high-risk patients who are already considered to have a poor prognosis.

### **Intramural Haematoma**

Intramural haematoma of the oesophagus is a rare complication of EIS and has a reported incidence of 0.3 to 1.6% (van Beljon 2004). The precise pathogenesis is speculative. Tissue necrosis extending into the submucosa and muscularis may be the initiating event and may be compounded by repeated injections (van Beljon 2004). Raised portal pressure and coagulation defects (Low 1988) may aggravate intramural dissection and extension of blood and sclerosant both longitudinally and circumferentially in the oesophageal wall (Jones 1986, Mosimann 1994). Tissue

necrosis is at its most severe during the first 3 to 4 days after sclerotherapy and this may explain the early manifestation of this complication (Salomez 1991). Other factors implicated in the pathogenesis include the different injection techniques (paravariceal versus intravariceal injection), the type of sclerosant solution, the volume of sclerosant given per injection, the interval between treatments and the occurrence of retching or prolonged valsalva during or shortly after injection sclerotherapy (Low 1988, Salomez 1991).

An intramural oesophageal haematoma should be suspected in a patient who presents with the triad of sudden onset dysphagia, odynophagia and haematemesis or blood stained sputum occurring soon after variceal sclerotherapy (Korula 1985, Ou Tim 1982, Shay 1981). There may however be no evidence of blood loss or haematemesis if the haematoma is contained within the oesophageal wall or submucosa and the mucosa has not been breached, in contrast to patients with a Mallory-Weiss tear who present with upper gastrointestinal bleeding with or without pain and no dysphagia (Thompson 1987). Associated retrosternal chest pain is common and is due to epithelial separation by the expanding intramural haematoma. The absence of subcutaneous emphysema in the neck differentiates this condition from the more serious complication of oesophageal perforation (van Beljon 2004).

In a patient who has recently had EIS and has a clinical presentation compatible with an intramural haematoma of the oesophagus, contrast studies provide the simplest way of confirming the diagnosis and excluding an oesophageal perforation (van Beljon 2004). A large elongated radiolucent intraluminal filling defect with a smooth outline is present on barium swallow which is best seen on the lateral view (Ou Tim

1982, Thompson 1987). The contrast study may also reveal a “double barrel” oesophagus in which contrast material can be seen in both the lumen of the oesophagus and in the intramural cavity (Benjamin 1965, Marks 1968). Oesophagoscopy is helpful in establishing the diagnosis but should be reserved for inconclusive cases because of the invasive nature of the investigation (van Beljon 2004). If performed, endoscopy usually shows a characteristic dark blue intramural bulge of mucosa (Ou Tim 1982). Other imaging studies that have been used include CT scan, MRI and oesophageal echo endoscopy.

Treatment depends on a definitive diagnosis of intramural oesophageal haematoma (van Beljon 2004). In contrast to patients with oesophageal perforation after EIS which has a poor prognosis and who may require urgent surgical intervention, patients with intramural haematoma have a good prognosis (Krige 1999). The initial treatment of intramural haematoma should be conservative (Reed 2001). Symptoms usually begin to resolve spontaneously within 36 – 72 hours and disappear completely in 2-3 weeks (van Steenbergen 1984). Patients should be kept nil per mouth and receive intravenous fluids. Oral feeds are introduced gradually as tolerated (van Beljon 2004). Resolution of the intramural haematoma occurs by reabsorption without disruption of the mucosal surface in patients with small haematomas or sloughing of the overlying mucosa may occur if the intramural haematoma is large (Ou Tim 1982, McGrath 1992). No adverse long term sequelae have been reported after intramural haematoma formation and in most cases oesophageal varices had disappeared and were absent on follow up oesophagoscopy (van Beljon 2004).

## **Stricture**

The incidence of oesophageal stricture after variceal sclerotherapy ranges from 11% to 58% (Krige 2005). In a prospective study of 204 patients undergoing long term sclerotherapy, the Cape Town group found that one in ten patients developed a stricture (Krige 2000). It is difficult to determine from published series precisely which factors contribute to stricture formation (Krige 1999b). Most reports have not found a direct relationship with number of sclerotherapy sessions, volume or type of sclerosant, and site of injection (van Steenberg 1984, Waring 1988, Snady 1984, Farrell 1992, Kochhar 1992). Sorensen et al., however, demonstrated a clear relationship between the frequency and cumulative volumes of injection and an association with pre-existing ulceration (Sorensen 1984). The 59% incidence of stenosis in 20 of 34 patients is among the highest reported. Their technique, however, differed from other studies. Paravariceal injections extending over the lower 10 cms of the oesophagus were performed every 3 days. Patients who developed strictures had received more injections and larger volumes of sclerosant, and a significantly greater number had preceding mucosal necrosis.

In the trial by Snady et al., patients undergoing sclerotherapy were randomised to receive either sclerotherapy plus acid protection (i.e. antacids, cimetidine, and sucralfate; 31 patients) or sclerotherapy alone (31 patients) (Snady 1984). In the former treatment group, 9.7% of patients developed symptomatic strictures during the course of treatment, compared with 38.7% of those who underwent sclerotherapy alone.

Sclerotherapy-induced strictures are usually short and localised to the lower 5 cm of the oesophagus. Most strictures can be dilated endoscopically without difficulty. Two to three dilatation sessions suffice for more than 85% of patients (Kochhar 1992). Persistent oesophageal dysmotility may explain the refractory dysphagia that occurs in some patients despite adequate dilatation. Dilatation does not precipitate bleeding from partially treated varices and although the stricture may temporarily delay eradication of varices, the sclerotherapy programme can be continued after stricture dilatation. For short, symmetrical strictures, Maloney mercury-filled rubber dilators allow easy and safe dilatation although tighter and longer strictures require fluoroscopically controlled dilatation over an endoscopically placed guidewire with Savary or Eder-Puestow dilators.

### **Motility disorders**

Several studies have evaluated the short and long term effects of sclerotherapy on oesophageal motor function and gastroesophageal reflux (Sauerbruch 1982, Reilly 1984, Larson 1984). Serial evaluation of motility patterns in the oesophagus before sclerotherapy, 3 days after sclerotherapy and 6 months later, has demonstrated that the length of the high pressure zone, peristaltic velocity and swallow-wave symmetry are markedly affected. The length of the high pressure zone increased significantly after the initial sclerotherapy session due to intense inflammation in the distal oesophagus. The normal waveform pattern and symmetry are altered considerably by sclerotherapy. Double- and triple-peak waveforms, dropped swallow waves in the distal oesophagus and simultaneous and spontaneous contractions have been observed (Reilly 1984, Larson 1984, Ogle 1978). Oesophageal scintigraphy of oesophageal function after eradication of varices has shown increased transit times

compared with controls (Spence 1990). These changes increase after sequential treatment and this effect probably is a manifestation of sclerosant-induced oesophagitis, intramural inflammatory response, or fibrotic changes in the oesophageal wall (Snady 1986).

Injection sclerotherapy has had no substantial effect on lower oesophageal sphincter pressure in most but not all studies (Reilly 1984, Larson 1984). In the study of Suzuki et al of lower oesophageal sphincter pressures measured in 41 patients before and after sclerotherapy, including measurement 6 months after treatment, the magnitude of the decrease in pressure was greater in patients with sclerotherapy-associated ulcers. The results showed correlation among the occurrence of reflux symptoms, ulceration, and decreases in sphincter pressure. However, these abnormalities were transient and had usually resolved by the 6 month follow-up examination (Suzuki 1991).

There is some discrepancy concerning the incidence and severity of gastroesophageal reflux after sclerotherapy and its effect on oesophageal acid clearance (Schuman 1985, Reilly 1984, Larson 1984, Ogle 1978, Cohen 1985, Shoenut 1986). Reilly et al. found that gastroesophageal reflux, as determined by standard reflux tests, becomes more prevalent after sclerotherapy and suggested that gastroesophageal reflux contributes to stricture formation (Reilly 1984). In contrast, Ogle et al. found no instance of acid reflux into the oesophagus although patients who received sclerotherapy did have impaired acid clearance (Ogle 1978). The magnitude of these changes are not thought to be severe enough to promote pathological gastroesophageal reflux. Sauerbruch et al. compared the results of

long term pH monitoring of 19 patients who underwent sclerotherapy and 15 untreated patients with cirrhosis who served as controls. There were no significant differences between the two groups with respect to percentage of time that oesophageal pH was less than 4 for the mean duration of reflux episodes (Sauerbruch 1993). In a similar study of 24 hour pH monitoring of 16 patients who underwent variceal sclerotherapy and 21 untreated patients with varices, Kinoshita et al. found a significant increase in the rate of gastroesophageal reflux in treated patients. The severity of reflux directly correlated with the volume of paravariceally injected sclerosant (Kinoshita 1992).

### **Other oesophageal complications**

A variety of unusual local oesophageal complications have been reported after sclerotherapy. Davion et al described the development of gastric bezoars in five patients undergoing sclerotherapy which was attributed to possible transient vagal nerve damage (Davion 1989). Pneumatosis intestinalis and pneumoperitoneum may occur due to intramural air entering through a small mucosal tear in the oesophageal wall and dissecting distally into the stomach, small bowel and colon. Rupture into the peritoneum produces free intraperitoneal air. The condition is benign and resolves spontaneously (DeMarino 1988). Other rare findings include pseudodiverticula (Scherl 1983), mucosal bridges (Gottfried 1985), and peri-oesophageal granulomas (Barsoum 1982). These findings are usually incidental and require no specific therapy.

Sporadic reports have described oesophageal carcinoma, usually the squamous cell variety, developing in patients undergoing sclerotherapy. These cases are few, and

additional risk factors (e.g. smoking, alcohol intake) can be identified in virtually all instances. Although surveillance of patients undergoing sclerotherapy has been recommended, there are no scientific data to support claims of a relationship between sclerotherapy and the development of carcinoma of the oesophagus (Krige 1999).

### **Cardiorespiratory effects**

Cardiac complications specifically related to variceal sclerotherapy are rare. Anecdotal accounts of coronary artery spasm (Charng 1988), persistent bradyarrhythmia (Perakos 1984), and heart failure due to polidocanol (Paterlini 1984, Imperiali 1986) have been reported. Seven cases of pericarditis after sclerotherapy have been described (Knauer 1987, Caletti 1990). Onset is heralded by fever, chest pain and dyspnoea. A pericardial friction rub is usually heard, and electrocardiographic and echocardiographic evidence point to a pericardial effusion. If pericarditis remains undiagnosed, progression to cardiac tamponade or constrictive pericarditis may occur (Brown 1987, Tabibian 1987). No precipitating factors have been clearly identified.

Pulmonary complications are common and range from minor asymptomatic changes found incidentally on routine chest x-ray films to aspiration or bronchopneumonia, pleural effusions, lobar collapse or consolidation and the adult respiratory distress syndrome (Barsoum 1982, Baydur 1990). It is often difficult to determine to what extent respiratory changes are directly attributable to sclerotherapy, because underlying parenchymal and vascular abnormalities are commonly found in chronic liver disease (Baydur 1990, Zeller 1991). Sepsis, pulmonary congestion due to fluid

shifts after vigorous resuscitation with crystalloids, massive transfusion, and diaphragmatic splinting by tense ascites are additional factors which may contribute to a deterioration in pulmonary function (Zeller 1991). In two cases described by Crawford and Ryan, acute respiratory insufficiency occurred after sclerotherapy. Both patients had ascites, and the respiratory difficulty was reversed by aspirating air from the stomach (Crawford 1984).

Several studies have investigated the distribution and potential damaging effects of sclerosant solutions on the respiratory system (Sukigara 1985, Connors 1986, DePuey 1988). There is evidence that sclerosant dissemination to the pulmonary and systemic circulation after intravariceal injection sclerotherapy occurs through oesophagogastric collaterals and the azygous-hemiazygous systems. Entry of sclerosant into the pulmonary circulation has been demonstrated to occur by positive uptake on lung scan of  $^{99m}\text{Tc}$ -labelled sodium tetradecyl sulphate and sodium morrhuate solutions when injected into oesophageal varices. Systemic dissemination has also been demonstrated to occur with ethanolamine oleate plus  $^{99m}\text{Tc}$  sodium pertechnetate, but the frequency and consequences appear to be minor (Sukigara 1985, Connors 1986, DePuey 1988).

Studies in experimental models, using large volume infusions of sclerosant solutions containing fatty acid derivatives (i.e., sodium morrhuate and ethanolamine oleate) injected directly into the right atrium, have produced pulmonary endothelial damage, transient increases in pulmonary artery pressure and haemorrhagic pulmonary oedema (Bailey-Newton 1985, Jones 1982, Spragg 1982, Ashbaugh 1968, Griffith 1979), with consequent significant worsening of gas exchange (Jones 1982). The

fact that oleic acid causes an acute pulmonary injury in animals has raised concern that variceal sclerosants containing fatty acids may cause similar injury in humans.

The pulmonary haemodynamic effects of sclerosant injection have been evaluated in several small clinical studies. Transient increases in pulmonary artery pressure from normal basal values occur during variceal sclerotherapy but are not associated with a change in cardiac output or arterial oxygenation (Glauser 1984). Intravariceal sclerotherapy using absolute alcohol results in significant mean pulmonary artery pressure increases at 1 and 5 minutes, with return to basal levels by 15 minutes. Equivalent volumes of saline produce similar significant rises in pulmonary artery pressure from basal levels, suggesting that the effect results from a volume load rather than the consequence of the sclerosant (Sarin 1988). Although pulmonary and systemic vascular resistance indices increase significantly from basal values after sclerotherapy with sodium morrhuate, pulmonary artery and pulmonary capillary wedge pressure remain stable without alterations in gas exchange (Bailey-Newton 1985). The changes in pulmonary haemodynamics after sclerotherapy in humans are small in magnitude and not sufficient to cause acute pulmonary capillary injury.

Because premedication and passage of an endoscope may contribute to aspiration pneumonitis or hypoxaemia, the incidence of respiratory dysfunction in patients receiving variceal sclerotherapy should be compared with those undergoing endoscopy for other reasons. In a controlled study Korula et al found no difference in either the short term or long term effects on lung function and gas exchange after sclerotherapy in patients with cirrhotic portal hypertension compared to a similar group undergoing diagnostic endoscopy only (Korula 1986). In contrast, Kitano et al.

found that patients complaining of post-injection retrosternal pain 24 hours after variceal sclerotherapy had a larger fall in vital capacity and forced expiratory volume than patients without pain (Kitano 1988). One third of cirrhotic patients with oesophageal varices were shown to have pre-existing pulmonary interstitial oedema and arterial hypoxaemia ( $Pa_{O_2} < 80$  mm Hg). In these patients, injection of 5% ethanolamine oleate may lead to further deterioration of pulmonary function and a decrease in arterial oxygen content (Kitano 1988). Samuels et al. found significant decreases in arterial oxygen tension and vital capacity in cirrhotic patients undergoing sclerotherapy. Samuels et al. suggested that these results indicated that sclerotherapy produced a restrictive defect in pulmonary function, possibly caused by embolisation of sclerosant to the lungs (Samuels 1994).

Pulmonary and mediastinal abnormalities are frequently found on routine chest x-ray and computed tomographic examinations when performed within 48 hours after variceal sclerotherapy. These changes may be explained by peri-oesophageal inflammation and by the fact that the oesophagus does not have the serosal layer that provides the barrier function for other organs. Saks et al. found radiological changes in 79% of patients after variceal sclerotherapy (Saks 1983). Pleural effusions and mediastinal soft tissue densities were the most common findings, and atelectasis, linear lung shadows and retrocardiac soft-tissue densities were demonstrated less often (Saks 1983, Mauro 1986).

Chest pain and effusions occur more frequently in patients who develop deep ulceration and are caused by an intense peri-oesophageal, mediastinal and pleural inflammatory reaction (Evans 1982, Ayres 1983, Bacon 1987). Most effusions are

small and resolve spontaneously. Pleural effusions were found by Bacon et al. after 31 (48%) of 65 sclerotherapy sessions performed in 30 patients (Bacon 1987). There was an approximately equal distribution between left-sided, right-sided, and bilateral effusions. The total volume of sclerosant injected was significantly greater in patients who developed effusions than in those who did not. Most of the effusions were exudative. Parikh et al. found pleural effusions in 6 of 31 patients who underwent sclerotherapy with absolute alcohol (Parikh 1993). As in the study by Bacon et al., chest pain, frequently persistent, was found to be significantly more common in patients with pleural effusions (Bacon 1987). Most effusions were small, developed within 48 hr of a treatment session, and disappeared without treatment within 1 week.

Aspiration is the most serious of the respiratory complications and occurs most frequently during sclerotherapy for acute bleeding. Aspiration pneumonia is avoidable if the stomach is emptied completely by suction before sclerotherapy is initiated and an assistant scrupulously clears the patient's mouth and hypopharynx with a suction catheter during the injection procedure. Excessive sedation, hepatic encephalopathy, and a prolonged procedure without adequate or effective airway protection during active bleeding are contributing factors if bleeding is massive. In this situation, endotracheal intubation before endoscopy is essential to avoid this potentially lethal complication.

Other uncommon pulmonary complications reported after sclerotherapy are broncho-oesophageal fistula (Carr-Locke 1982), pneumothorax (Alwmark 1982),

subcutaneous emphysema (Barsoum 1982), chylothorax (Gertsch 1983), and haemothorax (Rajagopalan 1994).

### **Systemic complications**

#### **Septicaemia and bacteraemia**

Transient fever due to an acute local inflammatory response or chemical phlebitis occurs in a fourth of patients after sclerotherapy. If a fever persists for more than 2 days, a search for a septic or local oesophageal complication is mandatory. Anecdotal reports have incriminated sclerotherapy as a cause of meningococcal and streptococcal pneumoniae septicaemia (Van Zaanen 1990), infective endocarditis (Baskin 1989), pyogenic meningitis (Kumar 1991), brain (Wang 1990, Robert 1991, Hassig 1992, Cohen 1985) and perinephric abscesses (Ritchie 1987) and bacterial peritonitis (Barnett 1987, Tam 1990). These reports have raised the question whether the incidence of septic complications are increased as a consequence of sclerotherapy-induced bacteremia.

There are several possible sources of bacterial contamination during injection sclerotherapy. The spectrum of organisms associated with bacteraemia and the predominance of alpha-haemolytic streptococci strongly suggest the oropharyngeal flora as the source of contamination. During sclerotherapy, these organisms may be introduced by the endoscope or injector needle and enter the bloodstream. The length of the needle injector and a contaminated water supply have been implicated in variceal sclerotherapy-associated bacteraemia (Snady 1985, Gerhartz 1984).

The incidence of bacteraemia after sclerotherapy ranges from 0% to 50% (Snady 1985, Gerhartz 1984, Cohen 1983, Camara 1983, Brayko 1985, Sauerbruch 1985, Low 1986, Hegnhøj 1988, Ho 1991). A variety of injection techniques, sclerosant solutions, and different lengths of injection needles were used in these studies. An increased incidence of bacteraemia occurs during and up to 5 minutes after sclerotherapy. Because blood cultures were drawn during both these periods in fewer than half of the studies, the extent of bacteraemia in some studies may have been underestimated. Inherent in all studies designed to search for positive blood cultures is the difficulty of determining true bacteraemia from contaminants. Some investigators have isolated common skin commensals, and in one study, 23% of isolates were coagulase-negative staphylococci (Sauerbruch 1985) which may originate from the skin during venepuncture.

Most previous studies and data on bacteraemia after sclerotherapy have been derived from blood cultures obtained during or after elective sclerotherapy. The risk of bacteraemia may be higher during the technically more demanding and traumatic emergency sclerotherapy and in the presence of venous and urinary catheters and endotracheal tubes. In the report of Bac et al., for example, the calculated risk for the development of bacterial peritonitis was significantly higher after sclerotherapy performed as an emergency than for elective procedures (Bac 1994). Patients with alcoholic cirrhosis may develop bacteraemia spontaneously because of decreased reticuloendothelial system function, impaired neutrophil chemotaxis, low levels of serum complement and impaired cell-mediated immunity (Ho 1991).

The incidence of infection after sclerotherapy was studied by Rolando et al. in a trial that compared sclerotherapy plus antibiotic prophylaxis (i.e. intravenous imipenem or cilastatin) with sclerotherapy alone in patients with variceal bleeding. No significant difference was found between the incidence of bacteraemia after treatment sessions in the control group and that in the patients who received antimicrobial prophylaxis (5.6% vs 1.1%). Most of the episodes of bacteraemia were associated with emergency treatment sessions (Rolando 1993). In a similar study by Pulanic et al., 30 patients with bleeding oesophageal varices underwent sclerotherapy without antibiotic prophylaxis, and 30 similar patients had sclerotherapy plus intravenous infusions of ampicillin with treatment and for 3 days thereafter. No significant differences between the two groups were found in the clinical parameters of infection (e.g., temperature, white blood cell count, differential blood cell count, erythrocyte sedimentation rate) during a follow-up period of 3 days (Pulanic 1989).

The clinical importance of blood culture isolates after sclerotherapy remains questionable. In none of the prospective studies have organisms (other than probable commensals) been isolated more than 30 minutes after sclerotherapy, suggesting that bacteraemia is always transient. No infective complications have been reported following bacteraemia in these studies. Previous recommendations advising routine antibiotic prophylaxis are no longer valid, and most authorities now recommend prophylaxis only for patients with specific vascular risk factors, such as prosthetic valves or previous episodes of endocarditis (Lorgat 1990). Strict attention to routine equipment cleaning and disinfection to avoid contamination of endoscopes and the water supply are essential.

### **Haemodynamic and thrombotic effects**

Potential effects of repeated long term after sclerotherapy and obliteration of oesophageal varices are an increase in portal pressure, the development of other compensatory collaterals, and bleeding from varices at remote sites (Manziona 1989, Foutch 1984, Korula 1991). Korula and Ralls demonstrated that, despite an improvement in laboratory and clinical parameters of hepatic function, the portal venous pressure gradient increased by a third in cirrhotic patients after eradication of oesophageal varices (Korula 1991). Dilawari et al. found that 6 (40%) of 15 patients with non-alcoholic portal hypertension developed spontaneous spleno-adreno-renal shunts after sclerotherapy (Dilawari 1989). The same mechanism may explain the increased incidence of portal hypertensive gastropathy after repeated sclerotherapy (D'Amigo 1990) and the phenomenon of bleeding from varices at other sites, including the umbilical vein (i.e. Cruveilhier-Baumgarten syndrome), duodenum, ileum, colon, rectum and bowel-related adhesions (Manziona 1989, Foutch 1984, Keane 1986, Fry 1988, Arst 1986, Elefthenadis 1988).

Changes and direction of flow in the coronary and azygos systems are complex in patients with portal hypertension. Phasic retrograde oesophageal collateral flow has been demonstrated during variceal sclerotherapy using fluoroscopy and endoscopic Doppler-flow techniques (Grobe 1984, McCormack 1983). Aoki et al. demonstrated by intra-operative portography that flow could be hepatofugal, to and fro, or hepatopetal (Aoki 1988). Altered venous flow, endothelial damage and a hypercoagulable state after repeated intravariceal sclerotherapy may promote excessive local venous thrombosis, with propagation into the splanchnic venous system and thrombosis of the portal and splenic veins. Some researchers maintain

that a local endothelial inflammatory response after variceal sclerotherapy is the initiating event, although others have shown that hypercoagulable states may be induced by sclerosant (Kang 1987, Musso 1987, Jacobson 1992).

In an umbilical cord model designed to simulate variceal blood flow, brief exposure to even low concentrations of sodium tetradecyl sulphate produces damage and stripping of endothelium, which exposes highly thrombogenic factor VIII-rich subendothelium (Jacobson 1992). The effects of sodium tetradecyl sulphate on coagulation and platelet function are dependent on sclerosant concentration. A dilute concentration of sodium tetradecyl sulphate induces a hypercoagulable state by selective inhibition of protein C and promotion of platelet aggregation. Activation of systemic blood coagulation in cirrhotic patients after sclerotherapy, which may be aggravated by vasopressin infusion, may promote venous thrombosis in the splanchnic bed. In experimental studies, higher concentrations of sodium tetradecyl sulphate inactivate the coagulation cascade and cause lysis of platelets (Jacobson 1992).

Because variceal sclerotherapy may lead to thrombosis of gastric varices (Kage 1987), it is conceivable that thrombus formation may extend further and initiate thrombosis in the splanchnic venous system. Portal vein thrombosis is a well recognised complication of cirrhosis and portal hypertension. The reported incidence ranges from 0.5% to 21% (Sarfeh 1979, Okuda 1985, Belli 1986). Acute portal or mesenteric venous thrombosis in association with variceal sclerotherapy is, however, uncommon. Nevertheless, a number of cases of portal or mesenteric venous infarction have been reported after variceal sclerotherapy or intravenous

administration of vasopressin (Thatcher 1986, Goldberg 1989, Ashida 1989, Deboever 1989).

In small retrospective series of patients undergoing portosystemic shunt surgery, Leach et al. found splanchnic venous thrombosis to be more common in patients who had prior sclerotherapy than in those who had no prior injection therapy (Leach 1989). Stoltenberg et al., in an autopsy series, demonstrated extension of thrombus from oesophageal varices into the portal and mesenteric venous systems that resulted in small intestinal infarction and hepatic failure (Stoltenberg 1987). In two cases, splenic vein thrombosis and splenic infarction occurred, suggesting propagation of clot through the coronary and left gastric veins. Rice et al. demonstrated clots in the portal venous system by means of Doppler sonography in patients who had undergone sclerotherapy or a portosystemic shunt operation, although this finding was relatively infrequent in the endoscopically treated patients compared with the surgically treated patients (i.e. end-to-side shunt 69%, distal splenorenal shunt 67%, sclerotherapy 5%) (Rice 1991).

Caletti et al. performed ultrasonography of the portal venous system in 25 patients before initiation of sclerotherapy and after obliteration of varices (Caletti 1987). They demonstrated no evidence of thrombosis or alterations in the calibre of the portal venous system. In contrast, Hunter et al. observed portal vein thrombosis in 36% of a small series of patients who had undergone sclerotherapy; controls had only a 10% incidence of such findings (Hunter 1988).

An increased incidence of thrombosis of the portal vein or its major tributaries after long-term sclerotherapy has been disputed. In the controlled trial of Kawasaki et al. comparing sclerotherapy with distal splenorenal shunt, all patients underwent angiographic assessment of the portal, splenic, and superior mesenteric veins before and after treatment. Those who received chronic sclerotherapy provided a unique group in which the incidence of thrombosis could be assessed. Despite frequent injections (mean 6.5) and large volumes (mean 62ml), no patient developed splenic or portal vein thrombosis (Kawasaki 1992).

Distant histological effects due to sclerosant, including intimal damage and fibrosis in the portal vein, have been reported after obliteration of oesophageal varices. Hunter et al. found substantial changes when comparing the morphology of portal and splenic veins in patients who had received variceal sclerotherapy with those who had not (Hunter 1988). In addition to the loss of smooth muscle and elastin fibres and medial fibrosis in patients with portal hypertension, those who had received variceal sclerotherapy also had disruption of normal venous architecture with loss of elastic fibres, smooth muscle bundles and an increase in fibrous tissue. Chaudhary et al. demonstrated changes in splenic vein histology in patients undergoing splenorenal shunt after variceal sclerotherapy, including increased fibrosis, intimal and medial destruction and microthrombi (Chaudhary 1990). Retrograde flow through collateral pathways or abnormal responses of the perivenous lymphatic vessels to the sclerosant may, alone or in combination, account for the observed changes (Hunter 1988).

Seidman et al. reported the case of a child who developed paraplegia after intravariceal injections of ethanolamine oleate. At autopsy 2 years later, the authors found evidence of an infarct of the spinal cord secondary to occlusion of the anterior spinal artery (Seidman 1984).

Several studies have demonstrated transient changes in the haemostatic mechanisms of patients undergoing sclerotherapy. In a study of 45 patients, Yamaga et al. found significant increases in concentrations of various fibrinopeptides and fibrin degradation products and observed suppression of platelet aggregation after intravariceal sclerotherapy using 5% ethanolamine oleate. Platelet function gradually returned to normal in approximately 1 week (Yamaga 1989). Ohta et al. found evidence of haemolysis, including haemoglobinuria, in patients undergoing sclerotherapy with 5% ethanolamine oleate; this finding was significantly more frequent in patients with albumin levels of less than 3.0 g/dl but was otherwise unrelated to liver function status. Haemolysis was found to increase with increasing concentrations of ethanolamine oleate and could be inhibited by increases in serum albumin. Creatinine clearance decreased in patients with haemoglobinuria, and two such patients developed acute renal failure (Ohta 1993). Miyoshi et al. found evidence of renal tubular dysfunction but no significant changes in glomerular filtration rate in patients undergoing sclerotherapy with ethanolamine oleate. Changes in renal function were suppressed by pretreatment with haptoglobin (Miyoshi 1991).

de Franchis et al. found that standard coagulation tests (i.e. prothrombin time, partial thromboplastin time, platelets, and fibrinogen) were not altered in patients undergoing

sclerotherapy with 5% sodium morrhuate plus thrombin or sodium morrhuate alone. However an abrupt increase in plasma fibrinopeptide A was demonstrated after sclerotherapy; in most cases, these levels returned to baseline within 24 hr. The authors suggested that sclerotherapy-related changes in coagulation were of no clinical significance (de Franchis 1987). However, Yuki et al. argued that mild transient symptoms such as headache and fatigue could be correlated with changes in coagulation parameters in patients who underwent sclerotherapy with a combination of hypertonic glucose, thrombin, and 1% polidocanol (Yuki 1991).

**Strategies to prevent endoscopic related complications:**

Endoscopic therapy is an established and integral part of the management of acute variceal bleeding and the long-term treatment of patients after a variceal bleed. Although complications after endoscopic therapy for variceal bleeding are common, most are minor and do not interrupt the treatment program (Krige 2005). In a small group of patients however, the success of therapy is compromised by recurrent bleeding and serious procedure-related complications. Most of the serious complications related to endoscopic therapy occur in patients with severe liver disease in whom control of bleeding is difficult. It is not the complication that is a breach of optimal care, but rather the failure to anticipate or recognize, and respond appropriately. Mature clinical judgment is necessary in acute problematic or complex cases and careful supervision of trainees or assistance by an experienced endoscopist becomes essential when critical decisions are required (Krige 1999). Early and close multidisciplinary consultation is often useful in demanding cases to facilitate appropriate therapy and optimal management.

A number of critical generic precautions are important to avoid both local and systemic complications, regardless of the type or technique of endoscopic intervention used to control acute bleeding. Effective resuscitation should precede endoscopy in patients with evidence of recent major bleeding. Diagnostic and therapeutic endoscopy should be performed in a well equipped unit with competent assistance and careful monitoring (Krige 2005). It is prudent to perform endoscopy with the minimum sedation needed for a safe procedure. High risk patients and those with significant cardio-pulmonary disease need only topical oropharyngeal anaesthetic spray and the minimum intravenous sedation. In a frail patient, a benzodiazepine alone may be safer than the combination of a benzodiazepine and an opiate (Krige 1996). Medications used for sedation should be titrated to the desired level of sedation using small, incremental doses. Flumazenil, a benzodiazepine antagonist, and naloxone, an opiate antagonist, must be available should a cardio-pulmonary complication occur. Meticulous attention should be given to suctioning of the mouth and hypopharynx by a dedicated assistant to avoid aspiration.

Early endotracheal intubation is crucial if major bleeding occurs. Precise and accurately placed injections are essential (Krige 2007). To ensure adequate visibility during active bleeding, a large or double channel endoscope with vigorous irrigation should be used with the head elevated. Uncontrolled blind, large volume injections during active bleeding must be avoided. The sclerotherapy needle should not exceed 5mm in length and a short bevel reduces the risk of deep injections and extravasation of sclerosant and injury to the underlying oesophagus. Recurrent bleeding after EIS requires careful evaluation and repeat endoscopy to determine

the source. If variceal bleeding continues or recurs during the index admission despite 2 adequate injections, other definitive therapy should be instituted.

If ulceration involves more than one oesophageal quadrant, further injections should be delayed until healing has occurred. Treatment with H<sub>2</sub>-blockers or sucralfate does not prevent ulceration, but may accelerate healing. Omeprazole has been effective in the treatment of chronic ulcers. Special care should be taken in patients with deep ulceration and persistent pain, fever, an increasing pleural effusion and deterioration of liver function which suggest transmural necrosis and impending perforation. Motility abnormalities are usually transient in nature and of minor clinical consequence and most symptomatic strictures respond effectively to dilatation.

In countries where cyanoacrylate adhesive is available and licensed for endoscopic use, damage to the endoscopic equipment, ulceration and pulmonary embolism, are the main potential complications that restrict its use. Damage to the endoscope is preventable if specific precautions are taken. There have been documented cases of cerebral, pulmonary and portal embolism. These complications appear to be related to the volume of cyanoacrylate injected. The volume should be limited to four to six ampoules (2.0–3.0g) per session.

Variceal eradication with endoscopic band ligation requires fewer endoscopic treatment sessions, and causes substantially less oesophageal complications (Tait 1999, Baron 2009). Although the incidence of early gastrointestinal rebleeding is reduced by endoscopic variceal ligation (EVL) in most studies, this does not result in an overall survival benefit relative to endoscopic injection sclerotherapy (EIS).

Simultaneous combination therapy (EVL+EIS) of large varices confers no advantage over EVL alone (Karsan 2005). A staged approach with initial EVL followed by EIS when varices are small requires further evaluation as the sequential combination may prove to be the optimal method of minimizing variceal recurrence (Krige 2005a). Overall, current data demonstrate clear advantages for using EVL in preference to EIS. EVL should therefore be regarded as the endoscopic technique of choice in the treatment of oesophageal varices (Krige 2005).

### **Conclusions**

Although complications after variceal sclerotherapy are common, most are minor and do not interrupt the injection programme. In a small group, however, the success of variceal sclerotherapy is compromised by recurrent bleeding and serious procedure-related complications (Schuman 1987). Most of the serious complications related to variceal sclerotherapy occur in patients with severe liver disease in whom control of bleeding is difficult. Several precautions are critical to avoid local and systemic complications. Effective resuscitation should precede endoscopy in patients with evidence of recent major bleeding. Diagnostic and therapeutic endoscopy should be performed in a well equipped unit, with competent assistants and careful monitoring. Meticulous attention should be given to suctioning of the mouth and hypopharynx by a dedicated assistant to avoid aspiration. Early endotracheal intubation is crucial if massive bleeding occurs.

Precise and accurately placed injections are essential. To ensure adequate visibility during active bleeding, a large or double channel endoscope with vigorous irrigation should be used, and the head of the patient's bed should be elevated. Uncontrolled,

blind, large-volume injections during active bleeding must be avoided. The sclerotherapy needle's length should not exceed 5 mm, and a short bevel reduces the risk of deep injections.

Recurrent bleeding after variceal sclerotherapy requires careful evaluation and repeat endoscopy to determine the source. If variceal bleeding continues or recurs during the index admission despite two adequate injections, other definitive therapy should be instituted. If ulceration involves more than one oesophageal quadrant, further injections should be delayed until healing has occurred. Treatment with H<sub>2</sub>-blockers or sucralfate does not prevent ulceration, but may accelerate healing. Omeprazole has been effective in the treatment of chronic ulcers. Special care should be taken in patients with deep ulceration and persistent pain, fever, an increasing pleural effusion and deterioration of liver function, all of which suggest transmural necrosis and impending perforation. Motility abnormalities are usually transient in nature and of minor clinical consequence. Most symptomatic strictures respond effectively to dilatation.

Mature clinical judgment is necessary in acute problematic or complex cases, and careful supervision of trainees by an experienced endoscopist becomes essential when critical decisions are required. Early and close multidisciplinary consultation is often useful in demanding cases to facilitate appropriate therapy and optimal management.

## **CHAPTER 3:**

### **PATIENTS AND METHODS**

#### **General management strategy**

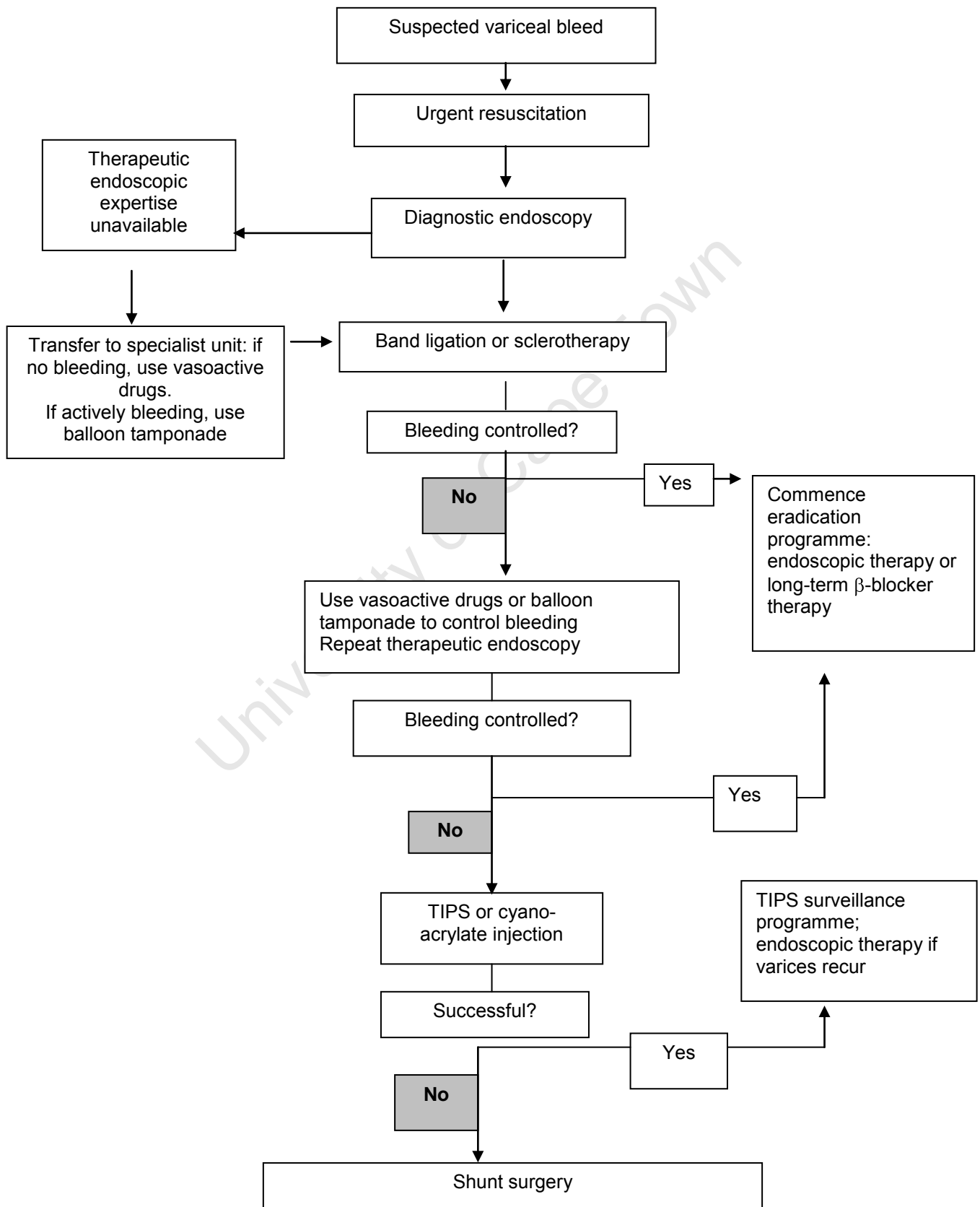
Patients who presented to Groote Schuur Hospital with a major upper gastrointestinal bleed were managed according to the specific upper gastrointestinal bleeding protocol used in the gastrointestinal clinic. In summary the protocol principles include urgent resuscitation and airway protection which took precedence over other investigations. Rapid and secure large bore peripheral venous access was obtained and intravenous fluid replacement initiated. Central venous access was obtained via an internal jugular vein in shocked patients. Standard blood component therapy including fresh frozen plasma and type O Rh-negative blood was given if required urgently before the availability of cross matched blood. Patients in whom oesophageal varices were suspected as the source of bleeding were rapidly resuscitated and underwent urgent endoscopy to identify the source of bleeding. Patients were nursed in an intensive or high care unit. The specific details of management have been published previously (Krige 2005, Krige 2007a, Krige 2007b, Krige 2009a). An outline of the management algorithm used is shown in Figure 1.

#### **Initial measures**

The extent and urgency of initial therapy depended on the severity of the gastrointestinal bleeding. Haemodynamically stable patients who were not actively bleeding or had stopped bleeding underwent urgent endoscopy and intervention in

the gastrointestinal clinic during office hours where the necessary endoscopic equipment required to control bleeding was available. Unstable patients who

**Fig. 1 Algorithm for management of acute variceal bleeding (Krige 2007a)**



continued to have major bleeding had the endoscopic intervention performed in the operating theatre. Patients who had massive or exsanguinating bleeding had a balloon tube inserted to control the acute bleeding before endoscopy was performed in the operating theatre. For emergency endoscopy in the operating theatre, a fully equipped and prepared mobile endoscopy stack was provided by the endoscopy staff. Emergency endoscopy did not commence until satisfactory venous access and central venous pressure lines were established and resuscitation procedures and volume replacement with blood transfusions were initiated to correct hypovolaemia. If bleeding was profuse or if the patient was encephalopathic, endotracheal intubation was performed before endoscopy was commenced to protect the airway and avoid aspiration.

Saline infusions were not used in order to avoid aggravation of ascites. Overzealous expansion of circulating blood volume was avoided to prevent precipitation of further bleeding. Central venous pressure was maintained at between 2 and 5 cm H<sub>2</sub>O, measured from the sternal angle. Patients who were haemodynamically unstable or elderly or had associated cardiac or pulmonary disease were monitored using a pulmonary artery balloon catheter to avoid excessive administration of fluids which, when combined with vasoactive drugs, would lead to the rapid onset of oedema, ascites and hyponatraemia. Clotting factors, if deficient, were replaced with fresh blood, fresh frozen plasma, vitamin K<sub>1</sub> and platelet transfusions. In patients with overt bleeding, octreotide was administered as an initial intravenous bolus dose of 100µg and then as a continuous intravenous infusion of 50µg per hour if bleeding continued despite injection sclerotherapy of the varices. All patients received oral

lactulose to minimize the onset of encephalopathy and intravenous antibiotics to prevent spontaneous bacterial peritonitis (Krige 2005, Krige 2007a, Krige 2007b, Krige 2009a).

### **Therapeutic intervention for variceal bleeding**

A standard injection sclerotherapy technique was used throughout the duration of the study (Krige 1994, Krige 1996). After intravenous sedation with midazolam, the diagnostic endoscopy and the variceal injection sclerotherapy was performed using a fiberoptic endoscope (model GIF 1T20 or K10; Olympus Corp, Lake Success, NY) during the first decade of the study and video-endoscopy during the last decade. The sclerosant, 5% ethanolamine oleate, was injected into the bleeding oesophageal varix using a combined intra- and paravariceal technique (Krige 1994). A maximum total volume of 25 ml of sclerosant was injected at any one endoscopy session for control of acute variceal bleeding or when large varices (grade 4 or 5) were encountered during elective sclerotherapy. An intravariceal technique alone with smaller total volumes of sclerosant was used for elective injection sclerotherapy when varices were grade 3 or less in size (Krige 1996). Endoscopic details including the location, size and extent of the varices, the site of active bleeding and the volume of sclerosant injected at each intervention were recorded.

### **Failure of emergency endoscopic therapy**

If a major variceal bleed recurred despite effective initial endoscopic and pharmacological therapy, the patient had an urgent repeat endoscopy and further injection of the bleeding site. If variceal bleeding was profuse and endoscopic injection was not possible or bleeding continued despite endoscopic intervention, mechanical control of the bleeding site by balloon tamponade was used. Any patient

who rebled after two successive emergency endoscopy treatments during a single hospital admission was recognized as having a prohibitively high mortality if further endoscopic therapy was pursued. These patients had a balloon tube inserted to control active bleeding, were resuscitated and then treated with a radiologically placed TIPS stent.

The initial and the second sclerotherapy injection session a week later were performed during the index admission to hospital. Subsequent injection sclerotherapy was undertaken at regular intervals at an outpatient clinic until the varices were eradicated. After variceal obliteration, surveillance endoscopy was performed at 3 and 6 months and then annually to identify patients in whom varices had recurred. Repeat injection sclerotherapy was performed whenever residual or recurrent varices were identified during surveillance endoscopy.

Once bleeding had been controlled, all patients had a comprehensive and detailed medical assessment which included documentation of clinical, biochemical and endoscopic factors which might influence or contribute to variceal rebleeding and mortality. A detailed history was obtained regarding the current or previous bleeding episodes, the duration and amount of alcohol intake, family history of liver disease or previous exposure to viral hepatitis. The physical examination documented the presence of stigmata of chronic liver disease including jaundice, peripheral and sacral oedema, spider angiomas, gynaecomastia, palmar erythema, testicular atrophy, white nails, Dupuytren's contractures, hypertrophic osteo-arthropathy, clubbing, foetor hepaticus, flapping tremor and curaneous purpura and petechiae. Abdominal examination documented the presence of a firm or hard nodular liver,

splenomegaly, ascites, caput medusa and Cruveilhier-Baumgarten syndrome with a para-xiphoid venous hum due to retrograde flow in a patent umbilical vein. The examination, in addition, sought to establish clinical evidence of encephalopathy, asterixis and cognitive dysfunction.

All patients had full laboratory studies including haematologic, biochemical and specific serologic testing. Patients' fluid and electrolyte status was evaluated by measuring serum electrolytes, urea and creatinine. Standard biochemical tests of liver dysfunction were measured including serum albumin, bilirubin, GGT, alkaline phosphatase, AST and ALT. All patients had hepatitis B surface antigen and anti-HBc core antigens tested. Hepatitis C was assessed by antibodies to HCV detected by enzyme linked immunoabsorbent assay. Positive results were confirmed by recombinant immunoblot assay. Patients with suspected primary biliary cirrhosis had their serum antimitochondrial antibody levels tested. Patients without an evident cause of cirrhosis were screened for haemochromatosis including serum ferritin and transferrin saturation levels, alpha-1-antitrypsin deficiency and Wilson's disease. Autoimmune hepatitis was tested by antinuclear and smooth muscle antibodies and serum IgG levels. In selected patients in whom a definitive diagnosis was unclear, a plugged liver biopsy were done and transjugular portal wedge pressures were measured. Transcutaneous abdominal ultrasound was done to assess liver size and appearance including the features of steatosis, cirrhosis or atrophy-hypertrophy complex, portal vein patency and diameter, direction of portal vein flow, spleen size and duplex Doppler assessment of portal flow velocity.

### **Data collection**

All study data, including the initial baseline and all subsequent follow-up clinical, haematologic, biochemical and endoscopic findings were recorded prospectively on a standard proforma for each patient and entered on a computer programme data base maintained by a dedicated research assistant. All patients in the study received their first emergency and all subsequent endoscopic variceal sclerotherapy injections in the unit. In order to assess risk factors for rebleeding and death in a defined population and to minimize possible confounding variables, only those patients who had bleeding oesophageal varices due to alcohol related cirrhosis and who were treated with injection sclerotherapy were evaluated and analysed in the following studies. Patients with non-alcoholic cirrhosis or other causes of portal hypertension as well as those treated by endoscopic variceal ligation were excluded from the analysis. The diagnosis of cirrhosis was established by clinical evaluation, laboratory data, findings on radiological imaging including ultrasound and portal venous doppler assessment, and in selected patients, liver biopsy and hepatic vein wedge pressure measurements. Cirrhosis was considered to be alcohol related if patients gave a history of sustained heavy alcohol consumption over several years and exclusion of other causes.

The analysis of all three studies was approved by the appropriately convened Departmental and Institutional Ethics and Research Committees of the University of Cape Town. Data validation and quality control procedures followed accepted international good clinical practice guidelines.

## **CHAPTER 4:**

### **VARICEAL RECURRENCE, REBLEEDING AND SURVIVAL AFTER LONG-TERM SEQUENTIAL ENDOSCOPIC INJECTION SCLEROTHERAPY IN 287 ALCOHOLIC CIRRHOTIC PATIENTS WITH BLEEDING OESOPHAGEAL VARICES**

#### **INTRODUCTION**

Cirrhosis is the third leading cause of death in urban males in the USA, and alcohol abuse is the leading aetiology (Orholm 1985, Grant 1991, Propst 1995). Major bleeding from oesophageal varices is the commonest cause of death in alcoholic cirrhotics who have portal hypertension with a reported mortality of up to 50% for the initial bleed and 30% for subsequent bleeds (Chedid 1991, Graham 1981, Saunders 1981, D'Amico 1995, Williams 1995). Endoscopic therapy is the emergency treatment of choice if actively bleeding oesophageal varices are present (Krige 2001, Krige 2009a, Terblanche 1994, Terblanche 1997). Even though the initial bleed may be controlled effectively by endoscopic therapy, the risk of subsequent rebleeding is substantial (Fleischer 1983, De Dombal 1986, Terblanche 1983, Terblanche 1985, Bendtsen 1996). There is general consensus that patients surviving a bleeding episode should be treated to prevent rebleeding (Terblanche 1988, Westaby 1992). An extensive body of evidence supports the use of repeated endoscopic treatment to obliterate oesophageal varices in order to prevent further variceal bleeding (Graffeo 1994, The Copenhagen Esophageal Varices and Sclerotherapy Project 1984, Westaby 1985, Korula 1985, Soderlund 1985, Kitano 1987, Terblanche 1989). Although banding of oesophageal varices is now regarded as the most effective endoscopic method of intervention (Tait 1999, Krige 2005), injection sclerotherapy is

still widely used to control oesophageal variceal bleeding as well as to eradicate varices to prevent rebleeding (Sorbi 2003). The major limitations of variceal injection sclerotherapy are recurrent variceal bleeds from residual varices prior to eradication, the cumulative risk of complications in patients having repeated injections (Krige 1999, Krige 2005, Terblanche 1994) and the fiscal and logistic implications (Terblanche 1990) because of the need for continued and prolonged surveillance endoscopy.

Despite the widespread use of endoscopic variceal treatment, data on long-term recurrence, rebleeding and survival after variceal eradication and the optimal frequency of endoscopic surveillance in alcoholic cirrhotic patients with bleeding oesophageal varices are limited (Pugh 1993, Waked 1997, Hartigan 1997, Tomikawa 2002). The present study evaluated the overall long-term clinical results of flexible injection sclerotherapy for a large cohort of consecutively treated alcoholic cirrhotic patients with endoscopically proven bleeding oesophageal varices followed prospectively in a single surgical unit. The data presented are based on a protocol using a standardised injection technique with eradication of oesophageal varices the predetermined end-point of repeated sclerotherapy (Krige 1994).

## **PATIENTS AND METHODS**

Consecutive adult alcoholic cirrhotic patients with endoscopically proven oesophageal variceal bleeding who were admitted to the surgical gastroenterology unit in Groote Schuur Hospital between January 1984 and December 2001 were assessed. All patients included in the study were either referred at the time of their first variceal bleed or after a proven variceal bleed and received their first emergency

endoscopic sclerotherapy injection in our unit. All injection treatments, both emergency and subsequent elective injections, were analysed to assess the role of sclerotherapy in long-term management. All patients were studied prospectively. As indicated in chapter 3, the diagnosis of cirrhosis was confirmed by findings on liver function tests, ultrasound and portal doppler assessment and, in selected patients, liver biopsy and hepatic vein wedge pressure measurements. Cirrhosis was considered to be alcohol related if patients gave a history of sustained heavy alcohol consumption over several years with corroborative histological evidence and exclusion of other causes.

During the 210 month study period, 378 consecutive adult alcoholic cirrhotic patients were treated for oesophageal variceal bleeding. Seventy two patients who had received variceal band ligation were excluded from the study group and the analysis. Nineteen patients who had cirrhosis and an alcohol history and in addition had positive viral markers were also excluded from the study. Data were analysed after a minimum 26 month follow-up period.

### **Technique of sclerotherapy**

A standard injection sclerotherapy technique was used as described in detail in the methods (Krige 1994, Krige 1996). After intravenous sedation with midazolam, diagnostic endoscopy and injection sclerotherapy was performed using either a fiberoptic endoscope (model GIF 1T20 or K10; Olympus Corp, Lake Success, NY) during the first decade of the study or video-endoscopy during the last decade. The sclerosant, 5% ethanolamine oleate, was injected using a combined intra- and paravariceal technique (Krige 1994). A maximum total volume of 25 ml of sclerosant

was injected at any one endoscopy session for control of acute variceal bleeding or when large varices (grade 4 or 5) were encountered during elective sclerotherapy. An intravariceal technique alone with smaller total volumes of sclerosant was used for elective injection sclerotherapy when varices were grade 3 or less in size. The initial and the second sclerotherapy session a week later were performed during the index admission to hospital. Subsequent sclerotherapy was undertaken at regular week intervals at an outpatient clinic until the varices were eradicated. After variceal obliteration, surveillance endoscopy was performed at 3 and 6 months and then annually to identify patients in whom varices had recurred. Repeat injection sclerotherapy was performed whenever residual or recurrent varices were identified during surveillance endoscopy.

### **Rebleeding**

Recurrent bleeding was defined as any episode of upper gastrointestinal bleeding that occurred after the first sclerotherapy session or subsequently between scheduled treatment sessions. All such bleeding episodes were investigated by emergency endoscopy, undertaken promptly after admission to hospital. Rebleeding was treated according to endoscopic findings. Additional sclerotherapy was undertaken if bleeding was due to patent residual or recurrent varices. Other sources of bleeding, such as peptic ulcers, gastric varices, erosive or haemorrhagic gastritis or portal hypertensive gastropathy were included in the definition of rebleeding. Eradication of varices was defined as the absence of oesophageal varices on repeat endoscopic examination during follow-up visits.

## **Survival Analysis**

Actuarial survival was calculated using the Kaplan-Meier method. Differences in survival in the three Child-Pugh grades were examined using the log-rank test. A p value less than 0.05 was considered significant. SAS System Package version 8.2 software (SAS Systems International, Cary, North Carolina, USA) was used for statistical analysis.

## **RESULTS**

The 287 patients evaluated in this study included 225 men and 62 women (mean age: 51.97 years; range: 24-87 years). Thirty nine patients were Child-Pugh grade A, 116 were grade B and 132 were grade C when assessed on first admission to hospital for variceal bleeding.

### **Recurrent bleeding before variceal eradication:**

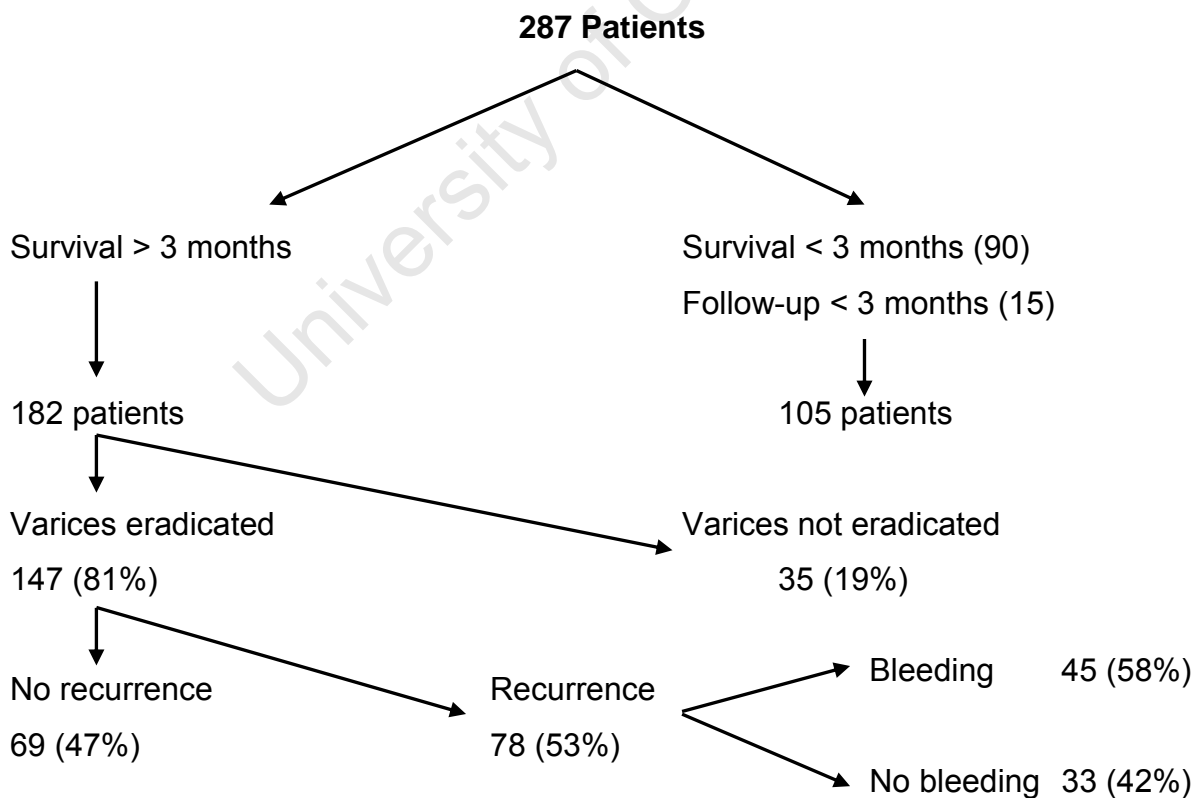
Rebleeding after the index injection procedure occurred in 104 of the 287 (36.2%) patients before eradication either during their index admission or after discharge from hospital. These 104 patients had a total of 170 bleeds during 164 subsequent admissions before the varices were eradicated. Ninety one patients bled from varices and 13 patients bled from non-variceal sources. The 91 patients had 124 variceal bleeds which were successfully treated with acute emergency injection sclerotherapy on 113 occasions. The remaining 13 bleeding episodes were from gastric varices (2), gastric erosions (1), portal hypertensive gastropathy (5), duodenal ulceration (1), Mallory-Weiss tear (1), bleeding oesophageal ulceration (1), oesophagitis (1), and one site was unknown. Mean survival in these 104 patients

(who rebled before eradication) was 23.8 months (median 8.1 months) with a mean survival in Child-Pugh grades A, B and C of 37.3, 37.6 and 11.0 months.

### Eradication of varices

Eradication and subsequent recurrence of oesophageal varices after sclerotherapy was assessed in 182 of the 287 patients who survived and who were followed up for more than 3 months (Fig. 4.1). Of the remaining 105 patients, 90 died within 3 months of entering the study and 15 patients did not complete the 3 month follow-up period. These 15 patients either moved abroad or lived far from our centre and attended other hospitals.

**Fig 4.1 Eradication and recurrence of oesophageal varices**



Oesophageal varices were eradicated in 147 of the 182 patients (80.7%) after a median of 4.9 injections (range: 1 to 14) during a mean of 7.1 months (median 4.6, range: 0.23 to 41.6 months) (Table 4.1). Mean survival in these 147 patients who had variceal eradication was 47.1 months (median 36.8 months) with the mean survival in Child-Pugh grades A, B and C of 40.2, 37.4 and 24.0 months. Oesophageal varices remained eradicated in 69 patients (mean follow-up from eradication: 34.6 months, median 23.6 months; range 1 to 174). Mean survival in these 69 patients in whom varices remained eradicated was 39.6 months (median 31.7 months) with the mean survival in Child-Pugh grades A, B and C of 47.5, 42.4 and 30.0 months.

**Table 4.1 Number of injections and time to eradication**

Child-Pugh Grade	Total number	Survival > 90 days	Number eradicated	Number of injections mean (range)	Months to eradicate mean (range)	Number recurred
A	39	37	26	4.8 (1-13)	9.0 (0.23-41.6)	7
B	116	90	78	4.9 (1-9)	9.4 (1.5-35.2)	26
C	132	55	43	4.2 (1-14)	5.2 (0.26-25.6)	12
Total	287	182	147	4.7 (1-14)	8.1 (0.23-41.6)	45

The 35 patients whose varices were not eradicated received a mean of 5.3 injections during a mean of 17 months. Twenty four of the 35 patients died (15 died of liver failure, 2 of bleeding oesophageal varices, 3 of hepatorenal failure, 2 of other causes

and in 2 patients the cause was unknown). Five patients were lost to follow-up and 6 patients in whom the varices were not eradicated were alive at the end of the study.

**Recurrent bleeding after variceal eradication:**

Forty five of the 78 patients with recurrence of oesophageal varices after eradication presented with variceal bleeding. This occurred after a mean of 16 months (range: 0.5 to 172 months). Nine of these 45 patients also had additional bleeding episodes from other sites following the first variceal rebleed after eradication (7 due to portal hypertensive gastropathy and 2 bled from gastric ulcers). Twenty two patients (48.8%) had several variceal rebleeding episodes.

**Oesophageal complications after sclerotherapy:**

The 287 patients received 353 emergency and 1015 elective injection treatments during a total of 2565 endoscopy sessions. Minor complications of sclerotherapy were common after acute injection for active bleeding and included dysphagia, transient fever and pulmonary atelectasis. A total of 747 complication events were documented in 234 patients during surveillance or unscheduled follow-up endoscopy after a prior variceal injection. If ulceration or stenosis was persistent and identified during a subsequent surveillance endoscopy session, this was documented as a separate additional event and recorded as such.

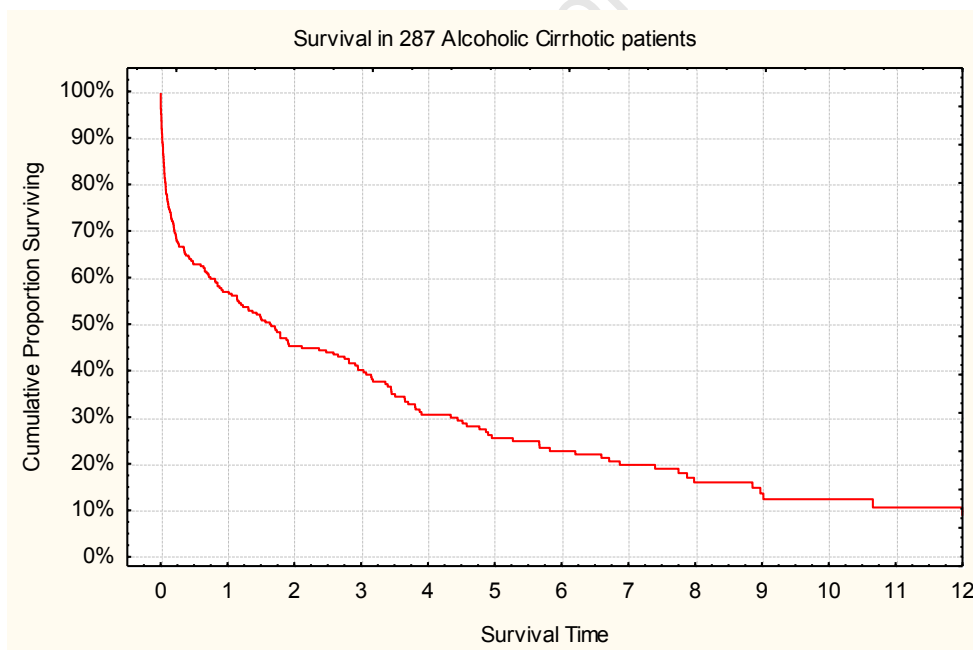
Mucosal ulceration at the injection site was found at follow-up endoscopy on 531 occasions in 199 patients. Subsequent sclerotherapy was delayed in patients who had mucosal ulceration involving more than one quadrant of the oesophageal circumference. An oesophageal stricture at the injection site occurred in 25 patients

after sclerotherapy, 9 of whom required oesophageal dilatation on 29 occasions with relief of symptoms. Two patients developed an intramural oesophageal haematoma after sclerotherapy which resolved on conservative therapy. Perforation of the oesophagus occurred in 8 patients as a consequence of repeated sclerotherapy to control of recurrent acute variceal bleeding. Five of these 8 patients survived, including 3 who required surgery to treat the complication.

### Survival Analysis:

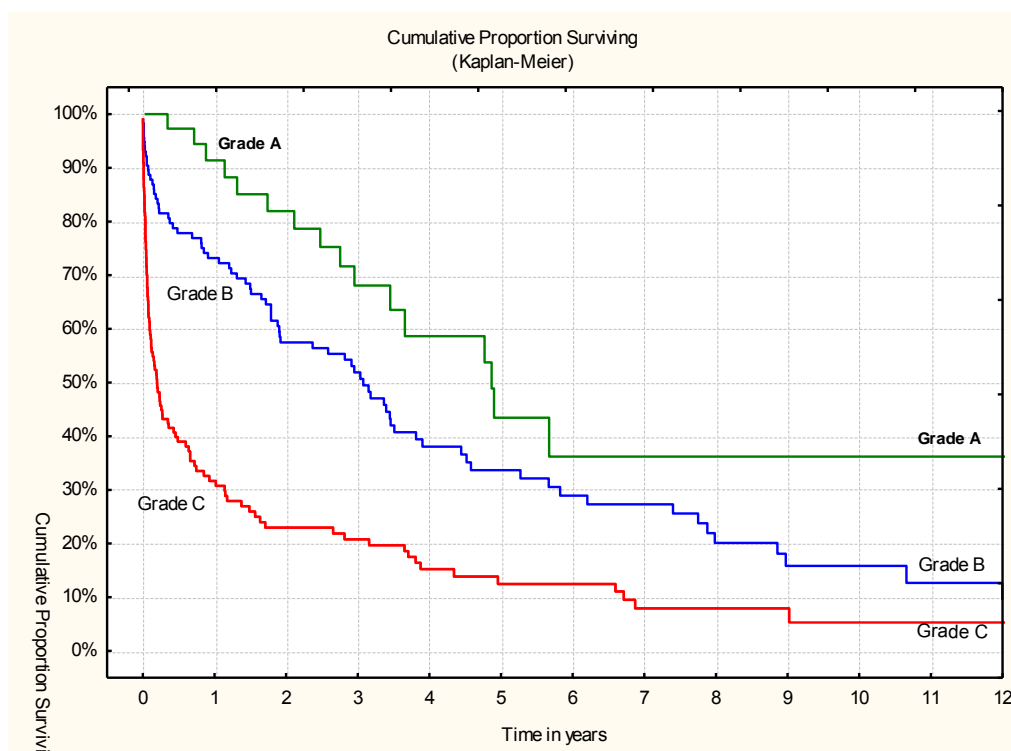
The cumulative survival of all 287 patients by life table analysis was 67% at 1 year, 42% at 3 years, 26% at 5 years and 13% at 10 years (Fig 4.2). Survival according to Child-Pugh grade A was 68 % at 3 years, 48 % at 5 years and 37% at 10 years.

**Fig. 4.2** Cumulative survival by life table analysis in all patients



Survival of Child-Pugh grade B patients at 3 years was 54 %, 34 % at 5 years and 17% at 10 years, and survival of Child-Pugh grade C patients was 21 % at 3 years, 13% at 5 years and 7% at 10 years (Fig 4.3).

**Fig. 4.3 Cumulative survival rates by life table analysis for patients at Child-Pugh risk grades A, B and C.**



Complete follow-up (median 32.3 months, mean 42.1 months, range 3-198.9 months) was achieved in 133 patients of the 182 patients who survived more than 90 days. In 49 patients follow-up was incomplete (median 30.1 months, mean 37.6 months, range 3.5-104.8 months).

#### **Causes of death:**

Two hundred and one (70%) of the 287 patients died during the course of the study. Liver failure was the commonest cause of death and occurred in 113 patients. Hepatorenal failure was the cause of death in 23 patients. Twelve patients died of

pneumonia, 37 of multi-organ failure, often precipitated by bleeding varices and 3 died of bleeding from other sites. Eleven patients died of other causes. These were carcinoma in 5 (lung 1, bladder 1, hepatocellular carcinoma 2, oropharynx 1), myocardial infarction 1, cerebrovascular accident 1, perforated gastric ulcer 1, acute pancreatitis 1, respiratory failure 1, motor vehicle accident 1. In 2 patients the cause of death could not be established.

## **DISCUSSION**

Alcoholic liver disease is a major cause of morbidity and mortality worldwide (Orholm 1985, Grant 1991). In Western countries, up to 50% of end-stage liver disease has alcohol as the main aetiological factor (Propst 1995). The mortality from alcoholic cirrhosis is higher than non-alcoholic cirrhosis and survival at 5 and 10 years is only 23% and 7% in some studies with 25% of patients dying within one year (Propst 1995, Chedid 1991). Thus the mortality rate of alcoholic cirrhosis is greater than many of the major categories of carcinoma such as breast, colon and prostate. Uncontrolled bleeding from varices and the consequences of ensuing liver decompensation are the commonest causes of death in alcoholic cirrhotics (Orholm 1985, Grant 1991, Propst 1995, Chedid 1991). Accurate long-term data detailing variceal recurrence or rebleeding after eradication, and survival in alcoholic cirrhotic patients are scant (Pugh 1993, Waked 1997, Hartigan 1997, Tomikawa 2002). In this prospective study, the long term efficacy of sclerotherapy was evaluated by using the specific endpoints of recurrent bleeding, variceal eradication, and survival in a large group of consecutive alcoholic cirrhotic patients treated at a single surgical centre.

Ultimate survival and outcome of treatment in this consecutive cohort of patients was disappointing. Although varices were eradicated in 82% of patients who survived more than 3 months, recurrent varices ultimately developed in 57% of patients, half of whom had further variceal bleeding. Several important and unresolved problems related to the role of repeated sclerotherapy in the long-term management of patients with oesophageal varices remain. There is increasing recognition that an important limitation of long-term sclerotherapy is the substantial incidence of rebleeding which is a particular feature of the early phase after endoscopic therapy has begun (Westaby 1985, Terblanche 1989). The most common source of recurrent bleeding before variceal eradication in this study was from patent residual varices which occurred in 31.7% of our patients in this study. Urgent repeat endoscopy is essential since in 87.5% of patients with recurrent bleeding, varices were the source and were treated by sclerotherapy which was effective in 113 variceal rebleeds in 91 patients. In 13 patients a non-variceal source of bleeding was identified. Serial sclerotherapy successfully eradicated esophageal varices in 80% of our patients. Although new varices formed following initial obliteration in 78 of 147 patients, this was associated with rebleeding in 45 of the 147 patients which would support the validity of the concept of variceal eradication as a specific endpoint of treatment.

The number of sclerotherapy sessions required to achieve variceal obliteration has varied considerably within reported series and between centres. While there is some evidence to suggest that the technique of injection sclerotherapy might affect the number of sessions necessary to achieve obliteration (Kitano 1987, Sorbi 2003), this alone does not explain the substantial differences found between patients. While the

risk of rebleeding diminishes with time as the variceal channels are obliterated, some recurrent bleeds are major and may contribute to deaths from liver failure. Any protocol for long-term endoscopic management of variceal haemorrhage requires a firm definition of treatment failure which allows alternative treatment options to be instigated. That such a definition is difficult to formulate, is reflected in the major discrepancies in the proportion of treatment failures in the larger controlled trials (Westaby 1992, Warren 1986, Rikkers 1987, Teres 1987). We believe that patients who develop life-threatening variceal bleeding after an adequate course of treatment should be regarded as failures of long-term treatment and in these a TIPS shunt gives the best results (Azoulay 2001). Other logistic problems with long-term sclerotherapy include the need for lifelong follow-up with repeated injections because varices recur in time. Surviving patients place an increasing burden on hospital resources, even when sclerotherapy is performed on an outpatient basis. In an analysis of the cost benefits of long-term endoscopic surveillance in a university-affiliated teaching hospital in Los Angeles of 324 patients who achieved variceal obliteration, 104 patients were followed up for >12 months (Waked 1997). In this cohort of 104 patients who were eligible for inclusion in the analysis, varices reformed in 73 patients (71%), mostly in the first year after obliteration or reobliteration. Nineteen patients (18%) had 23 rebleeding episodes. Survival was 84% and bleeding-related mortality was 6%. The annual cost of treating variceal reformers (\$2,117) was significantly higher than variceal nonreformers (\$1,735), but the overall cost of maintaining a patient on a chronic sclerotherapy program was relatively small. The authors concluded that the low rebleeding rate, the low mortality, and the relatively low cost in patients managed long term by chronic sclerotherapy underscored the benefits of this treatment program (Waked 1997).

Injection sclerotherapy is an invasive endoscopic procedure which requires a high level of manipulative skill and mature judgement. Complications related to injection occur mostly during acute major or recurrent bleeding when varices are large and the patient is restless or unco-operative (Krige 2000). The incidence of complications varies widely in reported studies because of variations in patient population, the type and severity of the underlying liver disease and the different injection techniques used (Krige 2000). In addition, the incidence of sclerotherapy-induced complications is higher when carefully documented in prospective studies (Krige 2005). In the present study, complications in the 287 alcoholic patients undergoing both emergency and elective sclerotherapy were frequent, occurring in a quarter of all sclerotherapy treatments and in more than two-thirds of patients overall. Asymptomatic oesophageal ulceration at the injection site was the most common complication and was detected at follow-up endoscopy. Ulceration is usually of little consequence in the overall management of the patient, but occasionally subsequent sclerotherapy had to be delayed. Our present policy is to use smaller volumes of sclerosant as varices decrease in size in an attempt to reduce the extent of ulceration. When ulceration involves more than one quadrant of the oesophageal circumference, further injection should be delayed until healing has occurred to prevent an oesophageal stricture (Krige 2007a, Krige 2007b). Serious complications were oesophageal strictures and perforation. Oesophageal stricture was significant and persistent in 9 of the 25 patients with this complication and all 9 responded to endoscopic balloon dilatation. Perforation of the oesophagus in this study was confined to emergency injection for complex recurrent bleeding (Goldberg 1995) and had a substantial mortality (Krige 2005).

Overall survival for the entire cohort was 42% at 3 years and 26% at 5 years. Even in Child-Pugh grade A patients there was an inexorable decline in the survival rate. Several factors including variceal size and wall tension, portal pressure gradient of >12 mm Hg and endoscopic variceal stigmata have been documented to predict the risk of bleeding and overall prognosis (Gluud 1988). The cause of portal hypertension, continued consumption of alcohol and the degree of liver decompensation are further important predictors of rebleeding and mortality (Madonia 2000, Vorobioff 1996).

An obvious shortcoming of this analysis is the lack of data detailing continued alcohol consumption, abstinence or recidivism and their relationship to rebleeding and survival. However, patients' voluntary admission or recall of continued alcohol use is notoriously inaccurate and may be unintentionally or intentionally misleading and was therefore not pursued in this study. Others have similarly indicated that any study evaluating continued alcohol consumption should be viewed with caution because of the difficulties in confirming abstinence (Orrego 1979). The adverse effects of alcohol on many tissues appear to be dose-related and abstinence at any stage in the disease should be encouraged. However, the benefits to be expected in term of rebleeding and mortality may be modest. Nevertheless, only abstinent patients are considered for liver transplantation in most major centers and this offers the best hope of improving long term prognosis in this patient group (Schenker 1990, Bird 1990).

The range of treatment options for bleeding oesophageal varices has expanded markedly during the past two decades. The treatment of acute and recurrent variceal bleeding is best accomplished by a skilled, knowledgeable, and well equipped team using a multidisciplinary integrated approach (Kriger 2005, Kriger 2009a). Optimal management should provide the full spectrum of treatment options including pharmacological therapy, endoscopic treatment, interventional radiological procedures, surgical shunts and liver transplantation (Sorbi 2003). Endoscopic variceal ligation has now replaced injection sclerotherapy in the elective treatment of esophageal varices in most centers. Data from randomised controlled trials show more rapid eradication of varices with lower rates of recurrent bleeding and fewer complications such as strictures and perforation (Tait 1999). However, a recent survey by the American College of Gastroenterology International GI Bleeding Registry shows that sclerotherapy is still used as frequently as banding for endoscopic intervention during index bleeding and more frequently than banding for control of variceal rebleeding (Sorbi 2003). Likely reasons include convenience, cost and widespread availability.

It is noteworthy that several recent randomised controlled trials comparing band ligation with sclerotherapy have reported a higher recurrence rate of varices in patients undergoing band ligation (Kriger 2005). If this observation is confirmed by further studies, the increased recurrence rate of varices may reduce or abolish the advantage of band ligation over sclerotherapy in the long term (Tait 1999). There is further evidence that endoscopic sclerotherapy is the more cost effective treatment per life-year gained if active variceal haemorrhage is present at the index endoscopy procedure (Gralnek 1999). This outcome appears related to the significantly higher

treatment failure rate experienced with endoscopic ligation for active variceal bleeding (Gralnek 1999). The long term data in this study has documented the variceal recurrence and rebleeding rate using a standard sclerotherapy technique. No comparable data exist for variceal ligation and ligation will require similar long term data to validate and vindicate its current status as the preferred endoscopic technique.

Our current management policy is for patients to have regular endoscopic therapy in order to achieve early variceal eradication, appreciating that factors such as oesophageal ulceration and poor patient compliance may interfere with the endoscopic therapy programme. After eradication of the varices, patients have surveillance endoscopy at six and then 12 month intervals and, if recurrent varices are identified, a comprehensive endoscopic treatment schedule is instituted again. Ultimately the use of sequential combined endoscopic techniques with variceal banding initially when varices are large followed by sclerotherapy when varices are small may enhance the endoscopic management of oesophageal varices both in terms of reducing complications, facilitating earlier eradication and preventing recurrence (Krige 2005, Krige 2009a).

## **CHAPTER 5:**

### **AN ANALYSIS OF EARLY REBLEEDING AND DEATH WITHIN 6 WEEKS OF INITIAL INTERVENTION IN 310 ALCOHOLIC CIRRHOTIC PATIENTS WITH ACUTE VARICEAL BLEEDING TREATED WITH EMERGENCY ENDOSCOPIC INJECTION SCLEROTHERAPY.**

#### **INTRODUCTION**

Variceal bleeding is the most serious complication of portal hypertension and substantially alters the natural history of patients with compensated alcoholic cirrhosis (de Franchis 2001, del Olmo 2000). Up to 20 per cent of initial bleeding episodes are fatal, and as many as 70 per cent of survivors have recurrent bleeding after a first variceal haemorrhage (Sharara 2001). Endoscopic therapy is the emergency treatment of choice if actively bleeding oesophageal varices are present (Sharara 2001, Krige 2005, Triantos 2006). Although advances in treatment (Baradarian 2004) have reduced overall mortality (Berry 2006, Chalasani 2003, Stokkeland 2006), uncontrolled or recurrent bleeding from varices and the consequences of ensuing liver decompensation remain the commonest causes of death in alcoholic cirrhotic patients (Le Moine 1992, Longacre 2006). Early rebleeding has been shown to be a strong predictor of mortality and recurrent variceal bleeding substantially increases the risk of complications which further contribute to mortality (Mihos 2004), emphasizing that rapid and sustained control of variceal bleeding remains the principal imperative of endoscopic intervention (Azoulay 2001).

There is international consensus that the assessment of the efficacy of treatment of bleeding oesophageal varices should be based on specific clinical outcomes (Thomsen 1998, de Franchis 1992, de Franchis 2005). These include the ability to achieve lasting haemostasis after the first variceal bleed, the risk of further variceal rebleeding, and death as a consequence of progressive liver decompensation (Thomsen 1998). In order to provide a consistent measure of standardisation and accuracy in the interpretation of data from different studies, specific and uniformly defined end-points which incorporate rebleeding and death have been formulated. The Baveno consensus conferences (de Franchis 1992, de Franchis 2005) have recommended that rebleeding within 5 days after the initial treatment should be used as the first end-point to assess initial control of bleeding. As the risk of rebleeding and death remains high during the initial phase after the first bleed, the time frame recommended for the second end-point, also incorporating rebleeding and death, is 6 weeks following the first admission to hospital (de Franchis 1992, de Franchis 2005, Pugh 1993).

Despite the widespread use of endoscopic therapy, few studies have specifically evaluated these endpoints in alcoholic cirrhotic patients with oesophageal varices (Pugh 1993, Hartigan 1997, Gluud 1988, Vorobioff 1996). Consequently, there is a paucity of accurate data on the efficacy of endoscopic control of bleeding, the frequency of early variceal rebleeding or survival in this high risk cohort. Published results are variable and conflicting because of small sample sizes, referral bias, dissimilar study end-points, differences in patient selection, methods and techniques of endoscopic intervention and the precise definition of rebleeding (de Franchis 1992, de Franchis 2005, Grace 1998). The objective of this prospective single

centre study was to evaluate the short-term efficacy at 6 weeks of flexible injection sclerotherapy in achieving control of acute variceal bleeding, and preventing rebleeding and death in a large cohort of consecutively treated alcoholic cirrhotic patients with bleeding oesophageal varices.

## **METHODS**

### **Patient population**

Consecutive adult alcoholic cirrhotic patients with endoscopically proven acute oesophageal variceal bleeding who were admitted to a surgical gastroenterology unit between January 1984 and December 2006 were assessed. All patients included in the study received their first emergency and all subsequent endoscopic sclerotherapy injections in our unit. As indicated in detail in the patients and methods section, all data were recorded prospectively on a standard proforma and entered on a computer programme maintained by a dedicated research assistant. The study analysis was approved by the appropriately convened Departmental and Institutional Ethics and Research Committees. Data validation and quality control procedures followed accepted international good clinical practice guidelines for the duration of the study.

During the 276 month study period, 632 consecutive adult patients were treated for oesophageal variceal bleeding in the unit. Two hundred and six patients had non-alcoholic causes of portal hypertension (53 had cryptogenic cirrhosis, 38 had hepatitis B-induced cirrhosis, 33 had extrahepatic portal vein thrombosis, 23 had cirrhosis secondary to chronic active hepatitis, and 59 patients had portal hypertension and varices due to other causes which included primary sclerosing

cholangitis, primary and secondary biliary cirrhosis, splenic vein thrombosis, Budd-Chiari syndrome and haemochromatosis) and were excluded from further analysis. The remaining 426 patients had portal hypertension due to alcohol-induced cirrhosis. Of these, 116 patients were not included in the study group because they had received endoscopic variceal band ligation during the initial 6 weeks after admission to hospital. Twenty nine patients who had cirrhosis and an alcohol history but in addition had positive hepatitis B or C viral markers were also excluded from the study group. Data in the remaining 310 patients with alcoholic cirrhosis and proven oesophageal variceal bleeding who received only sclerotherapy for bleeding form the basis of this study.

### **Clinical endpoints**

Control of variceal bleeding was evaluated at three time points; initial control during the first endoscopic intervention, variceal rebleeding within 5 days, before the start of long-term preventative therapy, and rebleeding within 6 weeks. The primary clinical endpoints of this study were (i) failure to control variceal bleeding during the first endoscopic intervention, (ii) early rebleeding (< 5 days) and later rebleeding (6 – 42 days) after initial endoscopic control, and (iii) mortality at 5 days and at 6 weeks. A secondary outcome of the study was assessment of the sclerotherapy-induced complications due to endoscopic variceal injection therapy which occurred during the first six weeks after the index bleed.

### **Technique of sclerotherapy**

The injection sclerotherapy technique used has been described previously in detail (Krige 1994, Krige 1996, Krige 2007a). Both diagnostic endoscopy and injection

sclerotherapy were performed using a fiberoptic endoscope (model GIF 1T20 or K10; Olympus Corp, Lake Success, NY) during the first decade of the study and video-endoscopy during the last decade. The sclerosant, 5% ethanolamine oleate, was injected using a combined intra- and paravariceal technique (Krige 1994, Krige 1996, Krige 2006a, Krige 2007a). A maximum sclerosant volume of 25 ml was injected at any one sclerotherapy session for control of acute variceal bleeding. A similar volume was used when large varices (grade 4 or 5) were encountered during subsequent elective sclerotherapy. An intravariceal injection technique with smaller total volumes of sclerosant was used for elective sclerotherapy when varices were grade 3 or less in size (Krige 1996, Krige 2006a, Krige 2007a). The initial and the second sclerotherapy session, a week later, were performed during the index admission to hospital. Subsequent sclerotherapy was undertaken at regular intervals on an outpatient basis until the varices were eradicated. Repeat injection sclerotherapy was performed whenever residual or recurrent varices were identified during surveillance endoscopy.

### **Rebleeding**

*Time zero* was defined as the time of admission to our hospital. *Failure to control bleeding* was defined as continued bleeding despite endoscopic injection, the addition of pharmacotherapy and the use of balloon tamponade. *Rebleeding* was defined as any episode of upper gastrointestinal bleeding that occurred after the initial bleed had been successfully controlled by sclerotherapy, or if bleeding occurred subsequently between scheduled treatment sessions. All such bleeding episodes were investigated by emergency endoscopy, performed promptly after admission to hospital. Rebleeding was treated according to endoscopic findings.

Additional sclerotherapy was undertaken if bleeding was due to patent residual varices. Other sources of bleeding, such as gastric and duodenal ulcers, gastric varices, erosive gastritis or portal hypertensive gastropathy were included in the definition of rebleeding. For the purposes of the study, patient data were evaluated for 42 days from the admission date, and all bleeding events and complications related to the sclerotherapy and deaths during this period were recorded.

### **Statistical Analysis**

Data were stored on a spreadsheet registry (Microsoft Excel, Redman, WA) and Stata software (Stata Corp 2003, Release 8, College Station, TX: StataCorp LP) was used for the statistical analysis. Descriptive statistical methods were used to determine 5 and 42 day rebleeding and mortality rates. Bivariate associations between categorical variables were analysed using the  $X^2$  test. The Kruskal-Wallis test was used to assess blood requirements in units of blood in each of the 3 Child-Pugh grades. For all analyses, a  $p$  value less than 0.05 and a 95% confidence interval that did not span unity were considered the thresholds of statistical significance.

## **RESULTS**

### **Patient demographics**

The 310 patients evaluated included 242 men and 68 women (mean age: 51.7 years; range: 24 - 87 years). Forty four patients were Child-Pugh grade A, 122 were grade B and 144 were grade C when assessed on their first admission to hospital (Table 5.1). Two hundred and thirteen patients required a blood transfusion during the initial hospital admission. Balloon tamponade with a Sengstaken-Blakemore or

Table 5.1

Child-Pugh grade, blood transfusion, balloon tube and vasopressin requirements to control acute variceal bleeding

Child-Pugh grade n= number of patients	A n = 44	B n = 122	C n = 144	Total n = 310	X <sup>2</sup> (d.o.f)	p-value
Number of patients requiring a blood transfusion	24 (54.6%)	78 (63.9%)	109 (75.7%)	211	8.51 (2)	0.014
Units of Blood: Range Mean Median	Range: 2 – 10 Mean: 4,4 Median: 4	Range: 2 - 42 Mean: 7,8 Median: 6	Range: 2 - 56 Mean: 10,8 Median: 6	Range: 2 - 56 Mean: 9.0 Median: 6	21.4 (2)	<0.001
Units of Blood 0 1 - 6 7 or more	20 22 2	44 47 31	35 57 52	99 126 85	19.46 (4)	<0.001
Balloon tamponade	1 (2%)	17 (14%)	26 (18%)	44 (14%)	6.90 (2)	0.032
Vasopressin / Octreotide	0	14 (11.5%)	29 (20.1%)	43 (13.8%)	12.40 (2)	0.002

Minnesota tube was used in 44 patients and vasopressin or octreotide was used in 43 patients (Table 5.1). Eighteen patients received both balloon tube and vasopressin. Significantly more Child-Pugh grade C patients required a major (>6 units) blood transfusion, the use of a balloon tube and vasopressin to control variceal bleeding (Table 5.1).

### **Day 0 to 5 rebleeding**

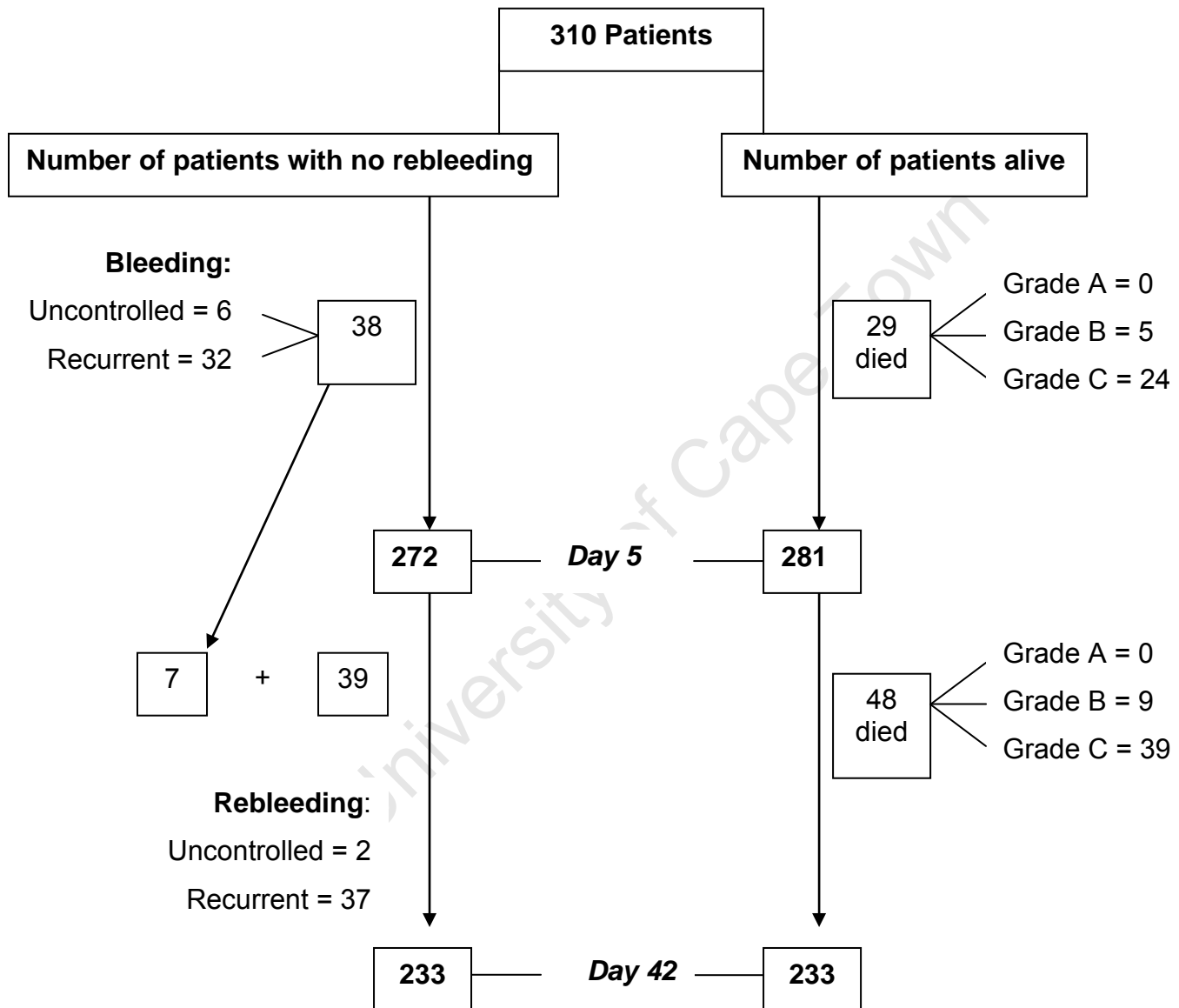
Emergency endoscopic injection sclerotherapy, supplemented with balloon tamponade when necessary, controlled acute variceal bleeding in 304 of 310 (98%) patients (Figure 5.1). In 6 (1.9%) patients, variceal bleeding was not controlled despite using pharmacologic and endoscopic therapy and balloon tamponade (Figure 5.1). A further 32 patients had recurrent variceal bleeding within 5 days of initial endoscopic control and required a further 39 emergency endoscopic variceal injection procedures (sclerosant volume: mean 16.1 ml, median 15 ml, range: 4 to 30 ml) to achieve definitive endoscopic variceal haemostasis. The 5 day endoscopic failure rate in achieving variceal haemostasis was 12.3% (38 of 310 patients).

### **Day 6 to 42 rebleeding**

Rebleeding after the initial 5 day assessment and up to 6 weeks after the index variceal injection occurred in 44 (15.7%) of the 281 patients who survived more than 5 days (Figure 5.1). Seven of the 44 patients had bled during the first 5 days and had further rebleeding episodes during this later period. These 44 patients had a total of 48 bleeding episodes and underwent a total of 83 repeat variceal injections (sclerosant volume range: 2 to 30 ml, mean 13.5 ml, median 12.3 ml) in the 6 to 42 day period. In this group 38 bleeding episodes were from varices and 10 from non-variceal sources including duodenal ulcer (n=1), portal hypertensive gastropathy

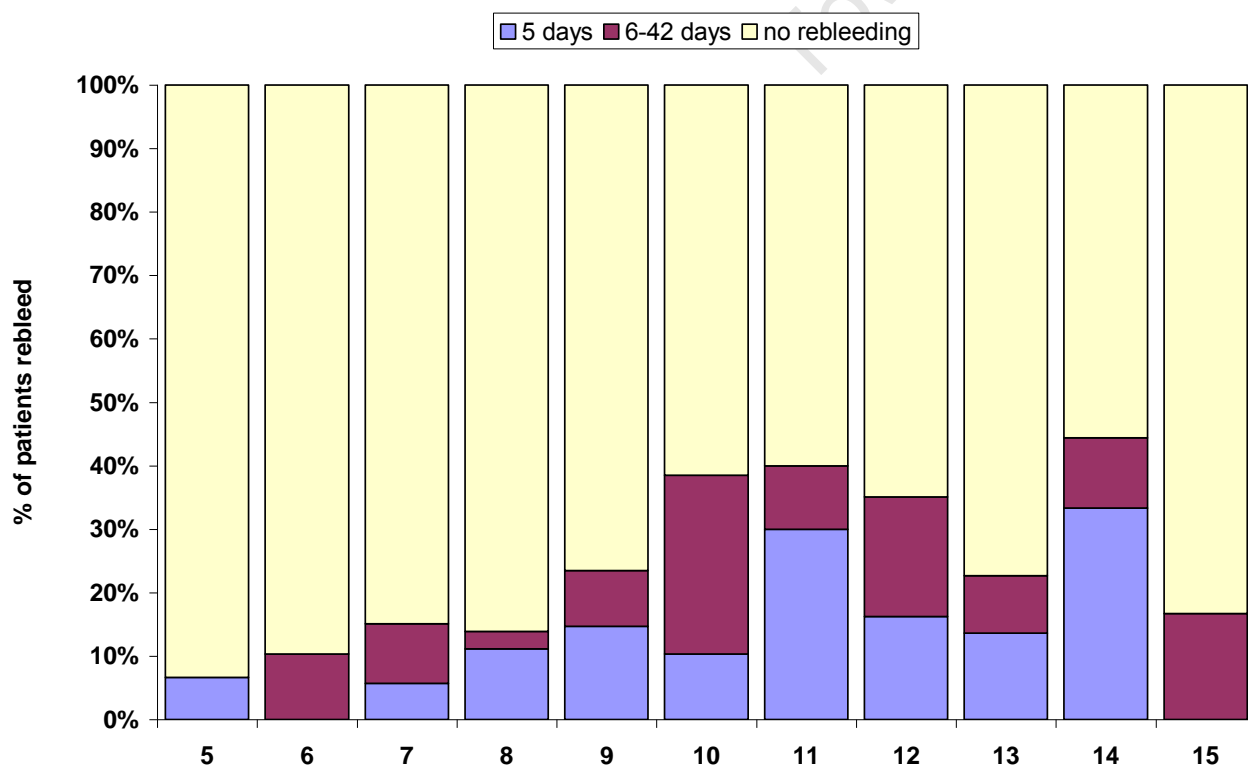
(n=2), Mallory Weiss tear (n=1), oesophageal ulceration (n=2), and 4 sites were not identified with certainty during endoscopy.

**Figure 5.1 Variceal rebleeding and death in 310 alcoholic cirrhotic patients**



Of the 44 patients who rebled, 13 (29.5%) died in the 6 week period. Overall 75 (24.2%) patients rebled during the 6 week assessment period after initial control during the index admission (Figure 5.1). The incidence of rebleeding increased according to the Child-Pugh scores. Twenty five (15%) of the 166 patients in Child-Pugh grades A and B rebled compared to 50 (34.7%) of the 153 patients in Child-Pugh grade C (Table 5.2). Significantly more Child-Pugh grade C patients rebled than Child-Pugh grade A or B patients ( $p < 0.001$ ) (Table 5.3).

**Table 5.2. Variceal rebleeding according to Child-Pugh Score**



Child-Pugh Grade	Grade A		Grade B			Grade C					
Child-Pugh Score	5	6	7	8	9	10	11	12	13	14	15
n	15	29	53	36	34	39	30	37	22	9	6
rebleeding	1	3	8	5	8	15	12	13	5	4	1
% rebleed	6.7	10.3	15.1	13.9	23.5	38.5	40.0	35.1	22.7	44.4	16.7

### Overall Mortality

Seventy seven patients (24.8%) died during the 6 week study period (Figure 5.1).

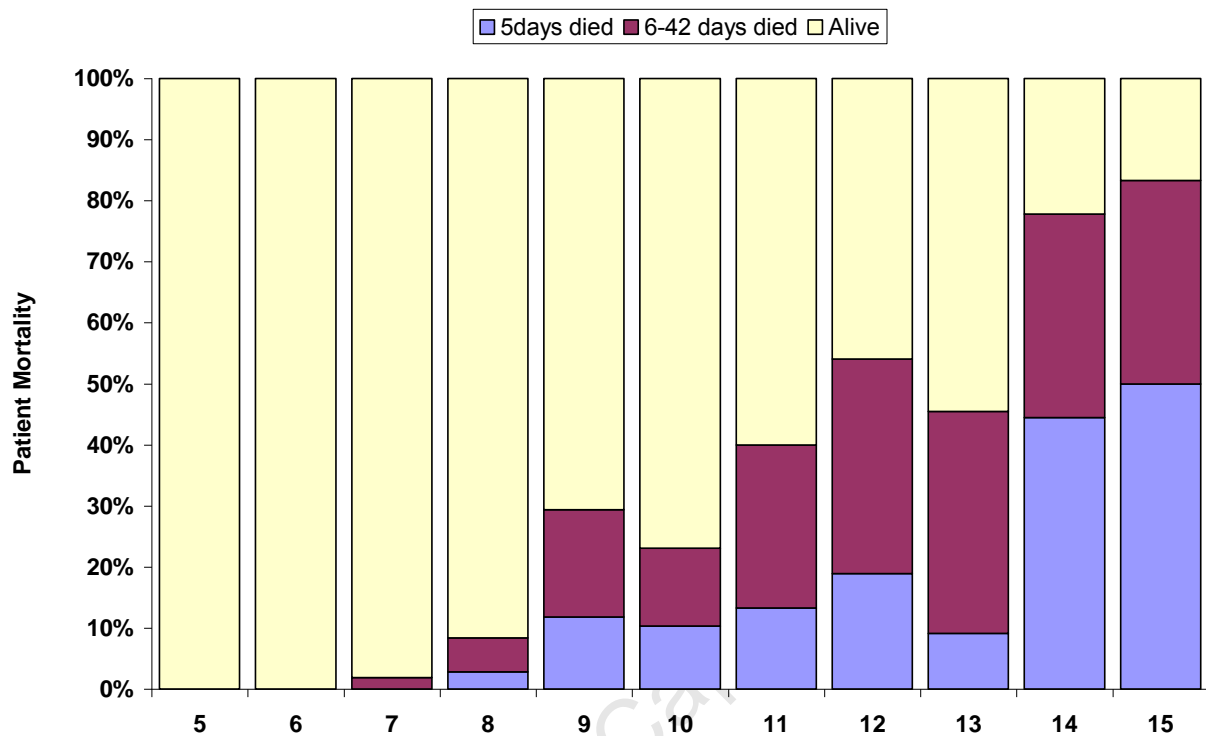
Twenty-nine (9.3%) died within 5 days of admission and 48 (15.4%) between day 6 and 42. No Child-Pugh grade A patients died, 14 Child-Pugh B patients died, and 63 Child-Pugh grade C patients died. Liver failure was the commonest cause of death and occurred in 29 patients. Twelve patients died of hepatorenal failure and 11 died of pneumonia and respiratory failure.

**Table 5.3 Rebleeding according to Child-Pugh grade**

Variable	Class	Total	Rebled <42 days	% Rebled	X <sup>2</sup>	P-value	Odds ratio	95% CI
Child-Pugh Grade	A	44	4	9%				
	B	122	21	17.2%				
	C	144	50	34.7%	17.41	<0.001	2.42	1.56 – 3.75

Death in 25 patients was a consequence of continued or recurrent variceal bleeding. Survival at 5 days and 6 weeks in Child-Pugh grade A patients was 100% and 100%, in Child-Pugh grade B patients 96% and 92.7%, and in Child-Pugh grade C patients 83.4% and 73%, respectively (Table 5.4). Significantly more Child-Pugh grade C patients died than Child-Pugh grade A or B patients (Table 5.5). Mortality increased exponentially as the Child-Pugh score increased with a mortality of 78% for a Child-Pugh score of 14 and 83% for a Child-Pugh score of 15 (Table 5.4).

Table 5.4 6 week mortality according to Child-Pugh Score



Child-Pugh Grade	Grade A		Grade B			Grade C					
Child-Pugh Score	5	6	7	8	9	10	11	12	13	14	15
N	15	29	53	36	34	39	30	37	22	9	6
Deaths	0	0	1	3	10	9	12	20	10	7	5
% deaths	0	0	1.9	8.3	29.4	23.1	40	54.1	45.5	77.8	83.3

Table 5.5 Mortality according to Child-Pugh grade

Variable	Class	Total	Died <= 42 days	% Died	X <sup>2</sup>	P-value	Odds Ratio	95% CI
Child-Pugh Grade	A	44	0	0				
	B	122	14	11.4%				
	C	144	63	43.7%	53.79	<0.001	6.91	3.79 – 12.58

### **Sclerotherapy related oesophageal complications**

The 310 patients received 786 injection treatments (342 emergency, 444 elective) during a total of 919 endoscopy sessions in the 42 day period. A total of 338 complications were documented in 159 patients during surveillance or unscheduled endoscopy after a prior variceal injection. Minor complications of sclerotherapy were common after acute injection for active bleeding and included dysphagia, transient fever and pulmonary atelectasis. Mucosal ulceration at an injection site was found at follow-up endoscopy on 333 occasions in 155 patients. An oesophageal stricture at the injection site occurred in 5 patients after sclerotherapy. None required oesophageal dilatation and all 5 resolved spontaneously. No intramural oesophageal hematoma or oesophageal perforations occurred in any of the 310 patients.

### **DISCUSSION**

This study used a large single centre dataset of alcoholic cirrhotic patients with portal hypertension and bleeding varices to assess the efficacy of endoscopic injection sclerotherapy in achieving primary haemostasis and preventing subsequent variceal rebleeding and death. The data demonstrated that endoscopic therapy was highly effective in controlling acute bleeding from oesophageal varices and that ultimate survival was influenced by both rebleeding and underlying liver reserve. Sustained control of acute bleeding has been shown to be a critical requirement in variceal management because each subsequent bleed worsens marginal liver function (Graffeo 1994). An analysis of data on death due to uncontrolled variceal bleeding which included 8 combined studies involving 1488 patients reported an 8% median mortality for exsanguinations which occurred within 48 hours of admission to hospital (D'Amico 2000, de Franchis 2007) In another recent survey death due to

uncontrolled bleeding occurred in 6.2% of patients (de Franchis 2007). However, despite urgent endoscopic and pharmacological therapy, variceal bleeding recurs in up to 20% of patients after the initial endoscopic intervention (Abralde 2007, Garcia-Tsao 2007). In addition, early variceal rebleeding significantly increases the risk of death within 6 weeks of the initial bleed (Abralde 2007, de Franchis 2007). Although initial endoscopic intervention controlled acute variceal bleeding in 98% of patients 10.3% rebled within 5 days and 24.2% rebled during the first 6 weeks. The 6 week rebleeding rate in the present study was higher than the 18.6% (D'Amico 2003a) and 19% (Graffeo 1994) reported by other authors probably because of two factors. This study had a strict prospective rebleeding definition and the study population consisted of a high risk alcoholic cirrhotic cohort. The incidence was similar to the 23% reported by Hartigan (Hartigan 1997), but significantly lower than the 31% rebleeding reported in an earlier study by Graham and Smith (Graham 1981).

It is clear from our observations and those of others (Jalan 2000, Garrett 1988, Thomopoulos 2006) that the efficacy of sclerotherapy in controlling acute oesophageal variceal bleeding and mortality from bleeding are closely related to the severity of the underlying liver disease. As anticipated, mortality in our study increased exponentially as liver reserve diminished. There were no deaths in Child-Pugh grade A patients and in this cohort with preserved liver function, early mortality was not influenced by the severity of the bleeding episode. Our data demonstrated that Child-Pugh grade C patients, who have the least hepatic reserve, were more likely to have a major bleed and require pitressin or octreotide and balloon tamponade in addition to sclerotherapy to control acute bleeding. We have shown in our study that in this high risk group, even when sclerotherapy successfully

controlled variceal bleeding, progressive liver failure resulted in high mortality rates in the first 6 weeks after admission, especially in patients with a Child-Pugh score >13 who subsequently had an 80% mortality.

Recent data show that mortality from variceal bleeding has decreased substantially from the 42% mortality reported in the seminal study by Graham and Smith in 1981 (Graham 1981) to current levels of around 20% (Abralde 2007). This significant improvement in survival reflects improvement in both the general management of severely ill cirrhotic patients and the treatment of hepatic decompensation which strongly influence the prognosis (Wiesner 2001). While it has been suggested that complications of portal hypertension, including variceal bleeding, are predictors of mortality in patients with liver cirrhosis, survival appears to be largely dependent on the severity of the underlying liver disease and it is now recognised that the degree of hepatic dysfunction is of overriding prognostic significance for patient survival (Wiesner 2001). Our study evaluated mortality at two time points: at 5 days when mortality is considered a direct consequence of the bleeding episode and at 6 weeks when mortality is a function of the adequacy of liver reserve. Overall survival for the entire cohort was 90.6% at 5 days and 75.2% at 6 weeks. The survival rate at 6 weeks in our cohort of decompensated alcohol-related cirrhotic patients was similar to the 23.6% (D'Amico 2003), 18.4% (Thomopoulos 2006), 19.0% (Graffeo 1994), 17.5% (Chalasanani 2003) reported by other authors, but higher than the 15.3% mortality reported by Boix et al. in 274 patients with cirrhosis of different aetiologies evaluated between 1997 and 2006 (Boix 2007).

Although several prognostic models have been proposed to predict mortality in patients with cirrhosis, the Child-Pugh score remains the most widely used scoring system both in clinical practice and in clinical research (D'Amico 2006) and is equal to or superior than other predictive systems in determining mortality within the first six weeks after a major variceal bleed (D'Amico 2006, Angermayr 2003, Garcia-Tsao 2008, Atkinson 2008, Sanders 2002). In a systematic review of 118 studies of cirrhotic patients, the most common independent predictor of death was the overall Child-Pugh score, followed by each of the five components of the Child Pugh score (D'Amico 2006). The advantages of the Child-Pugh score over more complex scores such as the Model for End-Stage Disease (MELD) score, is that the Child-Pugh score is simple and easy to use and can be calculated at the bed-side using mental arithmetic. Two significant flaws in the Child-Pugh score, however, are the subjectivity in the assessment of the degree of ascites and encephalopathy and the inability to distinguish mild from severe grade C patients with sufficient discrimination (Cholongitas 2005). The model for end-stage liver disease (MELD) score, which was originally designed for assessing the prognosis of cirrhotic patients undergoing transjugular intrahepatic portosystemic shunt (TIPS), is a continuous score relying on three objective variables. MELD has replaced the Child-Pugh score in Europe and United States for prioritising liver donor allocation according to a "sickest first" policy (D'Amico 2006). MELD best predicts 3 month survival of cirrhotic patients, irrespective of cause. MELD is based on creatinine, bilirubin, and international normalised ratio (INR) and is considered more reproducible because the components do not include subjective variables such as ascites and encephalopathy. However, both CP and MELD scores can vary substantially if single variables are modified by medical treatment such as an albumin infusion,

ascitic paracentesis, or overzealous diuretic therapy which can increase serum creatinine. In studies by Bambha and Chalasani, MELD was a clinically useful and objective predictor of short-term survival after acute variceal bleeding (Bambha 2008, Chalasani 2003). The Child-Pugh grade and scores in our study showed significant discrimination between grade A, B, and C patients and the incidence of rebleeding and death at 6 weeks.

Several important and unresolved issues relating to the specific roles of injection sclerotherapy compared to variceal banding in the management of patients with actively bleeding oesophageal varices remain. In most centres worldwide endoscopic variceal ligation has now replaced injection sclerotherapy in the elective treatment of oesophageal varices (Krige 2007a). Injection sclerotherapy is an invasive endoscopic procedure which requires a high degree of manual dexterity, skill and experience, especially during a major acute variceal bleed (Krige 2005, Krige 2007). Unlike endoscopic variceal band ligation, sclerotherapy is not standardised and there is wide variation in the injection technique, including the type and strength of sclerosant used, the method and frequency of injection, and the regularity of endoscopic surveillance (Jalan 2000, Krige 2007a). Data from randomised controlled trials of patients with acute variceal bleeding show equivalence between endoscopic variceal ligation and injection sclerotherapy in achieving initial haemostasis. Furthermore, randomised controlled trials indicate that ligation achieves more rapid eradication of varices with lower rates of recurrent bleeding and fewer complications such as strictures and perforation during elective therapy (Tait 1999). Despite these advantages, a survey by the American College of Gastroenterology International GI Bleeding Registry shows that sclerotherapy is still

used as frequently as banding for endoscopic intervention during index bleeding and more frequently than banding for control of variceal rebleeding (Sorbi 2003). The practical advantages of endoscopic sclerotherapy include its ability to achieve definitive control of variceal bleeding under direct vision, ease of use, convenience and low cost. A recent meta-analysis assessing emergency sclerotherapy for acute variceal bleeding in randomised trials suggests that sclerotherapy at the time of the initial endoscopy should remain the first choice therapy (Triantos 2006). An additional consideration reported in several randomised controlled trials comparing band ligation with sclerotherapy is a higher long term variceal recurrence rate in patients undergoing band ligation (Tait 1999). If this observation is confirmed by other studies, the consequences could reduce or even abolish the long term advantage of band ligation over sclerotherapy (Madonia 2000). The results of this study using sclerotherapy serve as the reference level for comparison by future endoscopic ligation studies.

A major strength of this study is that it was conducted in a single centre in a defined and homogenous population of consecutive patients using a uniform endoscopic injection technique which was supervised by the same group of investigators during the study period. In order to provide the highest possible level of uniformity and to minimise differences in the zero-time entry, only patients who presented with their first variceal bleed and received their initial and subsequent treatment in our unit were evaluated. The data were collected prospectively in this study and follow-up was complete with no patients lost. The study design minimized possible biases that may have resulted from patient selection, referral policies and local variations in treatment strategies. The use of rebleeding and death as the main outcomes

provided consistent and objective end-points in the study. The robustness of this study is enhanced by the prospective data collection, restriction of subjects to alcoholic cirrhotics and the complete follow-up of the cohort.

A number of limitations of this study are relevant. An obvious deficiency is the lack of data detailing continued alcohol consumption or abstinence in patients as a risk factor influencing survival. Previous studies by Vorobiof et al have described increases in portal pressure when alcoholic cirrhotics patients consume alcohol (Vorobiof 1996, Lucey 2008). In addition, Luca et al have shown that variceal bleeding in cirrhotic subjects has been linked with alcohol use (Luca 2007). Other investigators have reported that patients' voluntary admission or recall of continued alcohol use are notoriously inaccurate and may be misleading and was therefore not used as a variable in this study (Garcia-Pagan 2008). Another important aspect is that although the endoscopists and the technique of sclerotherapy remained constant, this study assessed patients over a 26 year period during which improvements in supportive care invariably would have occurred.

The results of our study clearly define the course and prognosis of patients with decompensated alcohol-related cirrhosis and bleeding varices. Despite substantial improvement in overall survival in recent years (Chalasani 2003, Carbonell 2004), the 6 week mortality after variceal bleeding remains discouragingly high, especially in Child-Pugh grade C patients (Thabut 2007) who succumb either from uncontrolled initial variceal bleeding or early rebleeding, or subsequently from the consequences of infection, liver and renal failure in the first weeks after a bleeding episode. As shown in this and other studies, most deaths were due not to bleeding, but to the

detrimental systemic consequences which lead to progressive deterioration of liver function (Thomopoulos 2006). The presence of advanced Child-Pugh score >13 in this study identified those patients at higher risk of dying. Our study confirms the observations of others (Hartigan 1997) that in experienced centres endoscopic injection sclerotherapy can be performed safely and effectively in alcoholic cirrhotic patients with actively bleeding oesophageal varices. However, even under optimal conditions, currently available treatment options fail to control initial variceal bleeding or prevent early rebleeding in up to 20% of patients, some of whom may require rescue intervention. Because most patients who fail first line endoscopic and pharmacological therapy are high risk and have marked liver decompensation complicating the variceal bleeding, TIPS has become the most widely used salvage therapy but still has an overall mortality in excess of 30% (Vangeli 2002). The essential future requirements necessary to improve survival in these high risk patients are self evident and include effective control of acute variceal bleeding, prevention of further rebleeding and minimizing deterioration of liver function. The early recognition of endoscopic failures and implementation of newer technologies for local control including self-expanding oesophageal metal stents (Zehetner 2008), enhanced efficacy of long-acting drugs (Lo 2008) and improved quality PTFE coated TIPS stenting (Bureau 2004) should provide better haemostasis in this high risk cohort.

## **CHAPTER 6:**

### **A MULTIVARIATE ANALYSIS OF PREDICTIVE RISK FACTORS FOR REBLEEDING AND DEATH IN ALCOHOLIC CIRRHOTIC PATIENTS WITH ACUTE VARICEAL BLEEDING TREATED WITH EMERGENCY ENDOSCOPIC INJECTION SCLEROTHERAPY**

#### **INTRODUCTION**

Bleeding from oesophageal varices is the most serious complication of portal hypertension and accounts for most cirrhosis-related deaths (Kriger 2005b). One quarter of cirrhotic patients who present with a major first variceal bleed, die as a consequence of the bleed (Kriger 2007a). Early mortality from uncontrolled bleeding ranges from 5 - 8% (Bosch 2003, D'Amico 2006). After control of the index bleed, there is a 70% chance of rebleeding with a similar mortality if further effective treatment is not given (Sharara 2001, Triantos 2006). Mortality is related to several factors including failure of rapid control of initial bleeding, early rebleeding, the presence and severity of underlying liver disease and the functional hepatic reserve (Burroughs 2008). Optimal emergency management requires an efficient and organised team to provide accurate initial assessment of the patient, effective resuscitation, rapid endoscopic diagnosis, successful intervention with control of bleeding, and prevention of early rebleeding as well as the anticipated complications of liver decompensation including spontaneous bacterial peritonitis, progressive liver and renal failure or hepatic encephalopathy (Kravetz 2007). The rational modern treatment of oesophageal varices requires a clear understanding of the risks of rebleeding, the hazards of liver decompensation and the likely response and benefits of further specific intervention (Henderson 1998).

Despite the widespread use of endoscopic therapy, few studies have provided robust prognostic factors which accurately predict rebleeding or death in alcoholic cirrhotic patients with bleeding oesophageal varices (D'Amico 2006, Garcia-Pagan 2008). Consequently there is no general agreement or international consensus which specific risk factors have the best prognostic value for early rebleeding and mortality after variceal bleeding. Published results are variable and conflicting because of small sample sizes, referral bias, dissimilar study end-points, differences in patient selection, techniques of endoscopic intervention and the precise definition of rebleeding. In addition, the spectrum of variables and differences among alcoholic cirrhotics make formulation of a prognostic model complicated. To overcome the complexities of these variations, a large data base is required which includes the outcome variable and the intervention components and variables for each patient (Christensen 1997). The objective of this study was to identify by multivariate analysis and internal validation the prognostic variables predicting rebleeding and death at 6 weeks in alcoholic cirrhotic patients admitted to hospital with a first variceal bleed.

## **PATIENTS AND METHODS**

### **Patient population**

The patient information for this study was obtained from the prospectively collected database and included consecutive adult patients with endoscopically proven acute oesophageal variceal bleeding who were admitted to the surgical gastroenterology unit between January 1984 and December 2006 and who were enrolled in a longitudinal observational study. All study data were recorded on a standard proforma and entered on a computer programme maintained by a dedicated

research assistant. In order to assess risk factors in a defined population and to minimize possible confounding variables, only those patients with bleeding oesophageal varices due to alcohol related cirrhosis who were treated with injection sclerotherapy were analysed. All patients received their first emergency and all subsequent endoscopic variceal sclerotherapy injections in our unit. Patients with non-alcoholic cirrhosis or other causes of portal hypertension as well as those treated by endoscopic variceal ligation, were excluded from the analysis to maintain a homogenous cohort. The diagnosis of cirrhosis was established by clinical evaluation, laboratory data, findings on radiological imaging including ultrasound and portal venous doppler assessment, and in selected patients, liver biopsy and hepatic vein wedge pressure measurements. Cirrhosis was considered to be alcohol related if patients gave a history of sustained heavy alcohol consumption over several years and exclusion of other causes.

### **Therapeutic intervention for variceal bleeding**

All patients with haematemesis underwent urgent upper gastro-intestinal endoscopy soon after admission and resuscitation to identify the source of bleeding and were treated with injection sclerotherapy if bleeding oesophageal varices were found. The injection sclerotherapy technique used has been described in detail previously (Krige 1996, Krige 2007, Krige 2006). Patients with haemodynamic instability or a significant drop in haemoglobin level (<8g%) were given a packed red cell transfusion to a haemoglobin level of 10g% and the blood volume transfused was recorded. The initial and the second sclerotherapy session, a week later, were performed during the index admission to hospital. Endoscopic details including the size of varices, the presence of active bleeding and the volume of sclerosant injected

at each intervention were recorded. Subsequent sclerotherapy was undertaken at regular intervals at an outpatient clinic until the varices were eradicated.

### **Data Collection**

All patients had a complete medical assessment at their initial presentation to hospital including documentation of clinical, biochemical and endoscopic factors that might contribute to variceal rebleeding and mortality. To identify potential risk factors related to rebleeding and death, a retrospective analysis of the prospectively collected data was performed. Fifteen variables related to clinical and biochemical data, as well as details of the endoscopic intervention including size of varices and sclerosant volume, were analysed.

### **Data Synthesis and Analysis**

The primary endpoints of the study were rebleeding and death at 42 days. *Time zero* was defined as the time of admission to our hospital. *Failure to control bleeding* was defined as continued bleeding despite endoscopic injection and the addition of pharmacotherapy and the use of balloon tamponade. *Rebleeding* was defined as any episode of upper gastrointestinal bleeding that occurred after the initial bleeding episode had been successfully controlled by sclerotherapy, or bleeding that occurred subsequently between scheduled treatment sessions. *Mortality* was defined as death from any cause. The study design and analysis was approved by the appropriately convened Departmental and Institutional Ethics and Research Committees. Data-validation and quality-control procedures followed accepted international good clinical practice guidelines.

Continuous variables were dichotomised on the basis of existing literature (Pugh 1973). Tested variables included albumin level (<25 vs >25 g/L), INR (<2.3 vs >2.3), total bilirubin level (<51 vs >51  $\mu\text{mol/L}$ ), ascites (nil and mild vs moderate and severe) and encephalopathy (nil and mild vs moderate and severe), variceal size (grade 1,2,3 vs 4,5) and sclerosant volume given per sclerotherapy session (1-15 vs 16-30 ml). The categorical variables included gender, age (<60 years vs >60 years), pitressin, the need for balloon tube tamponade. and number of variceal sclerotherapy injections used to control the acute bleed (1 vs >1).

### **Statistical Analysis**

Bivariate associations between categorical variables were analysed using the  $\chi^2$  test. The Kruskal-Wallis test was used to assess blood requirements in units of blood in each of the 3 Child-Pugh grades. Logistic regression was used to estimate odds ratios (OR) with 95% confidence intervals (CI) for adjusted and unadjusted effects. Initially each risk factor was examined independently which produced the unadjusted OR and 95% CI. The significant candidate variables identified by univariate analysis underwent multivariate logistic regression analysis to produce a prognostic model ("the training set") representing rebleeding and death in the first 6 weeks after admission to hospital. The performance and discriminative ability of the constructed models to predict rebleeding and mortality at 6 weeks was assessed using receiver operating characteristic (ROC) analysis. The prediction accuracy was quantified using the concordance index (C-index) which is equivalent to the area under the ROC curve and reflects the ability of a model to discriminate participants (or patients) who develop the event of interest (i.e. rebleeding or death) from those who do not. Values range from 0.5 to 1; a value of 1 is indicative of a model with perfect

predictive power. For all analyses, a  $p$  value less than 0.05 and a 95% confidence interval that did not span unity were considered the thresholds of statistical significance. Stata software (Stata Corp 2003, Release 8, College Station, TX: StataCorp LP) was used for statistical analysis.

### **Validation process**

The developed models were tested for validity and concordance in a further set of alcoholic cirrhotic patients with bleeding varices (“the test set”). Model discrimination between the training (derivation) set and the test (validation) set was evaluated using the C statistic.

## **RESULTS**

### **Patient characteristics**

During the 276 month study period, 632 consecutive adult patients were treated for bleeding oesophageal varices. Patients with non-alcoholic causes of portal hypertension ( $n=206$ ) or who had received endoscopic variceal band ligation ( $n=116$ ) were not included in the study. The remaining 339 patients had portal hypertension due to alcohol-induced cirrhosis. Of these, 29 had cirrhosis and an alcohol history, but in addition had positive hepatitis B or C viral markers and were also excluded from the study group. Data in the remaining 310 patients with alcoholic cirrhosis and proven oesophageal variceal bleeding who received only endoscopic injection sclerotherapy for bleeding form the basis of this study.

The 310 patients (242 men, 68 women) had a mean age of 51.7 years (range: 24-87) and underwent 786 endoscopic variceal injection treatments (342 emergency,

444 elective) during 919 endoscopy sessions in the 6 week period after the first variceal bleed. Forty four (14.2%) patients were Child-Pugh grade A, 122 (39.4%) were grade B and 144 (46.4%) were grade C when assessed on their first admission to hospital. Two hundred and eleven patients required a blood transfusion during the initial hospital admission. Balloon tamponade was used in 44 patients and vasopressin or octreotide was used in 43 patients. Eighteen patients required both balloon tube and vasopressin.

## **Outcome**

### **6-week rebleeding rate**

Emergency endoscopic injection sclerotherapy, supplemented with balloon tamponade when necessary, controlled acute variceal bleeding in 304 of 310 (98%) patients. In 6 (1.9%) patients, the initial acute variceal bleeding was not controlled despite using pharmacologic and endoscopic therapy and balloon tamponade. Overall 75 (24.2%) patients rebled during the 6 week assessment period after initial control during the index admission.

### **Overall Mortality**

Seventy seven patients (24.8%) died during the 6 week study period. Twenty-nine (9.3%) died within 5 days of admission and 48 (15.4%) died between day 6 and 42. Liver failure was the commonest cause of death and occurred in 29 patients. Twelve patients died of hepatorenal failure and 10 died of pneumonia and respiratory failure. Death in 25 patients was a consequence of either continued or recurrent variceal bleeding.

## **Rebleeding and mortality analysis**

### **Factors related to variceal re-bleeding within 6 weeks**

Univariate analysis was used to determine the unadjusted risk factors for rebleeding and death. When predictors of rebleeding during the first 6 weeks were considered, logistic regression analysis found that >6 units of blood transfused, the presence of ascites and a bilirubin level >51 mmol/L were the best set of significant predictor covariates (Table 6.1). However, in the final stepwise multivariate logistic regression analysis model, only two variables, bilirubin levels greater than 51 mmol/L and >6 units of blood transfused during the initial hospital admission were significant predictors of rebleeding (Table 6.2).

### **Factors related to 6-week mortality after variceal bleeding**

Univariate logistic regression analysis found that >6 unit blood transfusion, pitressin or octreotide infusion, the presence of encephalopathy and ascites, the need for a balloon tube to control acute bleeding, a prolonged INR >2.3, a low serum albumin level <2.5g/L, and increased bilirubin levels >51 mmol/L were significant predictors of death at 6 weeks after the initial variceal bleed (Table 6.3). In the final multivariate logistic regression analysis model, six variables, encephalopathy, ascites, bilirubin levels >51 mmol/L, a prolonged INR >2.3, an albumin level <25 g/L and the need for balloon tube tamponade were significant predictors of death within the first 6 weeks (Table 6.4).

### **Validation of study data**

The validity of the models identified from the multivariate analyses for rebleeding and death at 6 weeks in the 310 study patients (“the training set”) were tested against

another 55 alcoholic cirrhotic patients treated subsequently in our unit (“the test set”). The data are shown in the receiver operating characteristic (ROC) curves in figures 6.1 and 6.2.

**Table 6.1 Univariate analysis of categorical variables predicting variceal rebleeding**

Variable	Class	Total	Rebleed	% Rebleed	X <sup>2</sup>	P-value	Odds Ratio	95% CI
<b>Gender</b>	Male	242	58	24%				
	Female	68	17	25%	0.03	0.860	1.05	0.56 – 1.97
<b>Age</b>	<=60 years	226	52	23%				
	>60 years	84	23	27.4%	0.63	0.424	1.26	0.71 – 2.23
<b>Blood Transfusion</b>	<=6 Units	128	44	34.4%				
	>6 Units	85	31	36.5%	9.62	<b>0.002</b>	2.36	1.36 – 4.09
<b>Bilirubin (µmol/l)</b>	<=51	186	35	18.8%				
	>51	124	40	32.3%	7.32	<b>0.007</b>	2.05	1.21 – 3.47
<b>Albumin (g/l)</b>	>=25	251	57	22.7%				
	<25	59	18	30.5%	1.58	0.208	1.49	0.79 – 2.79
<b>INR</b>	<=2.3	284	69	24.3%				
	>2.3	26	6	23.1%	0.01	0.890	0.93	0.36 – 2.42
<b>Ascites</b>	1, 2	166	30	18.1%				
	3	143	45	31.5%	7.50	<b>0.006</b>	2.08	1.22 – 3.53
<b>Encephalopathy</b>	1, 2	239	52	21.7%				
	3	70	23	32.8%	3.62	0.057	1.75	0.97 – 3.16
<b>Variceal grade</b>	1, 2, 3	191	41	21.5%				
	4, 5	119	34	28.5%	2.01	0.155	1.46	0.86 – 2.47
<b>Pitressin</b>	No	267	61	22.8%				
	Yes	43	14	35.6%	1.90	0.168	1.63	0.81 – 3.27
<b>SBTube</b>	No	266	60	22.6%				
	Yes	44	15	34.1%	2.73	0.098	1.77	0.89 – 3.52

**Table 6.2 Multivariate logistic regression model for rebleeding**

<b>Risk factor</b>	<b>P-value</b>	<b>Odds Ratio</b>	<b>95% CI</b>
<b>Bilirubin <math>\geq 52 \mu\text{mol/L}</math></b>	0.025	1.85	1.08 – 3.16
<b>Blood transfusion &gt; 6 Units</b>	0.008	2.14	1.22 – 3.76

The area under the ROC curve for each model in the test set was not significantly different from the corresponding area in the training set, indicating that the predictive sensitivity and specificity observed in the training set were accurately reproduced in the test set. The concordance (c)-statistic yielded values in the model for death which ranged from 0.84 to 0.87 indicating a robust model with good predictive accuracy (Fig 6.1). The model predicting the likelihood of death at 6 weeks was expressed as a box plot showing the distribution of the predicted probabilities of death (Fig 6.2). The calculated threshold for death in the box plot was 30% with the proposed model accurately predicting a high risk of dying in those patients above the 30% threshold. The concordance (c)-statistic in the model for rebleeding at 6 weeks was less predictive with values ranging from 0.56 to 0.63 indicating that the selected variables in the proposed model for variceal rebleeding at 6 weeks were less likely to identify those patients who might rebleed than those likely to die (Fig 6.3). Similarly, the box plot (Fig 6.4) indicated that the proposed model for rebleeding was less accurate at predicting those patients who were likely to rebleed within the 6 week period, suggesting that the candidate variables selected by uni- and multivariate analyses, which mainly represented liver function, were more accurate in predicting survival than rebleeding which may be related or dependent on additional unrecognised or untested factors.

**Table 6.3 Univariate analysis of categorical variables predicting death**

Variable	Class	Total	Died <= 42 days	% Died	$\chi^2$	P-value	Odds Ratio	95% CI
<b>Gender</b>	Male	242	63	26%				
	Female	68	14	20.5%	0.84	0.359	0.73	0.38 – 1.41
<b>Age</b>	<=60 years	226	55	24.3%				
	>60 years	84	22	26.2%	0.11	0.737	1.10	0.62 – 1.95
<b>Blood Transfusion</b>	<=6 Units	225	41	18.2%				
	>6 Units	85	36	42.4%	19.24	<b>&lt;0.001</b>	3.29	1.90 – 5.70
<b>Bilirubin (<math>\mu\text{mol/l}</math>)</b>	<=51	186	25	13.4%				
	>51	124	52	41.9%	32.35	<b>&lt;0.001</b>	4.65	2.67 – 8.07
<b>Albumin (g/l)</b>	>=25	251	48	19.1%				
	<25	59	29	49.1%	23.07	<b>&lt;0.001</b>	4.08	2.24 – 7.44
<b>INR</b>	<=2.3	284	60	21.1%				
	>2.3	26	17	65.3%	24.99	<b>&lt;0.001</b>	7.05	2.99 – 16.61
<b>Ascites</b>	1, 2	166	19	11.4%				
	3	143	58	40.5%	34.80	<b>&lt;0.001</b>	5.27	2.94 – 9.45
<b>Encephalopathy</b>	1, 2	239	36	15%				
	3	70	41	58.5%	54.78	<b>&lt;0.001</b>	7.97	4.40 – 14.42
<b>Variceal grade</b>	1, 2, 3	191	41	21.5%				
	4, 5	119	36	30.3%	3.03	<b>0.082</b>	1.58	0.94 – 2.67
<b>Pitressin</b>	No	267	54	20.2%				
	Yes	43	23	53.5%	21.95	<b>&lt;0.001</b>	4.53	2.32 – 8.86
<b>SBTube</b>	No	266	50	18.8%				
	Yes	44	27	61.4%	36.64	<b>&lt;0.001</b>	6.86	3.47 – 13.54

**Table 6.4 Multivariate logistic regression model for death**

Risk factor	<i>P</i> -value	Odds Ratio	95% CI
Encephalopathy Grade 3	<0.001	5.69	2.78 – 11.63
Ascites Grade 3	0.011	2.52	1.23 – 5.16
Bilirubin $\geq 52 \mu\text{mol/L}$	0.012	2.40	1.12 – 4.80
INR $\geq 2.3$	0.003	4.93	1.70 – 14.24
Albumin $\leq 24 \text{ g/l}$	0.012	2.58	1.23 – 5.40
Balloon tube tamponade	<0.001	8.60	3.67 – 20.17

**Figure 6.1 The ROC curves of the models generated with the Training and Test data for predicting 6 weeks mortality in patients with variceal bleeding**

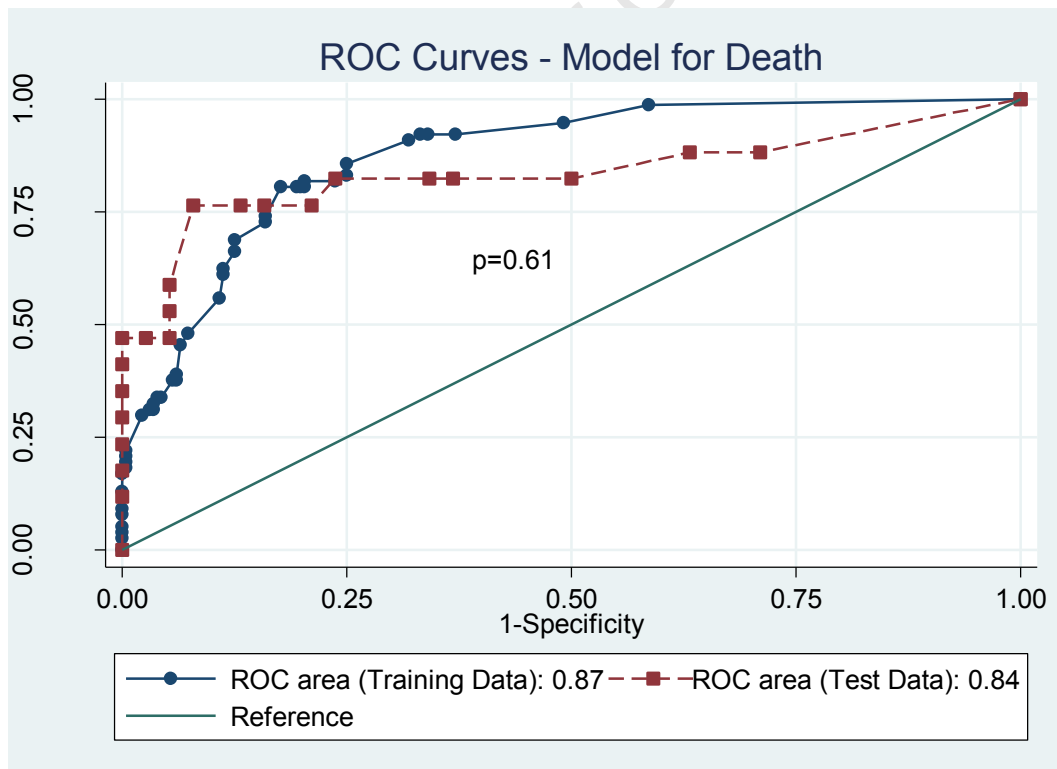


Figure 6.2 Box Plot of predicted probability for death

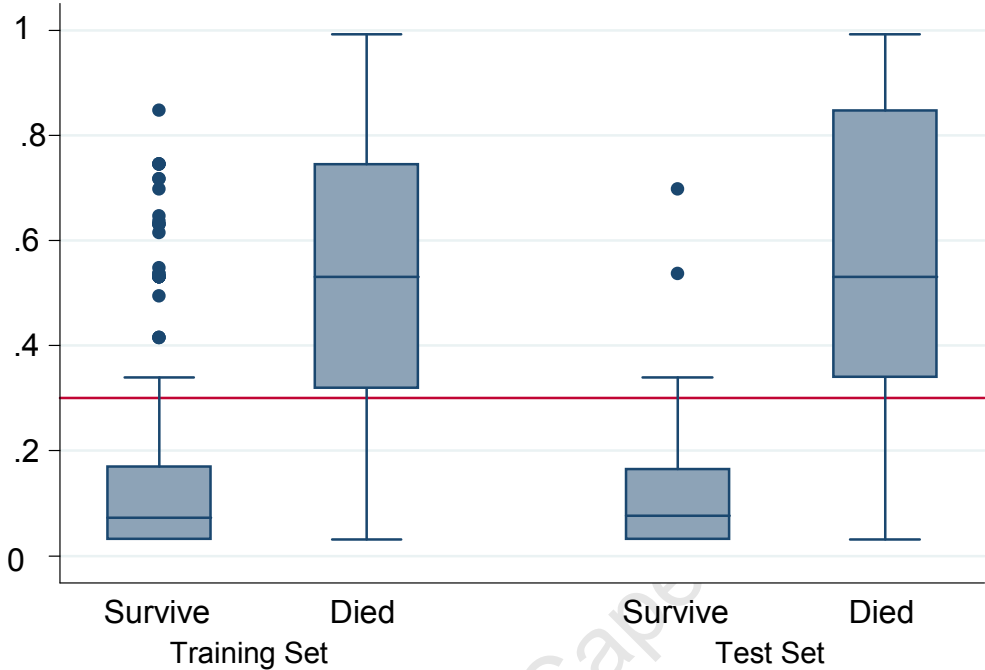
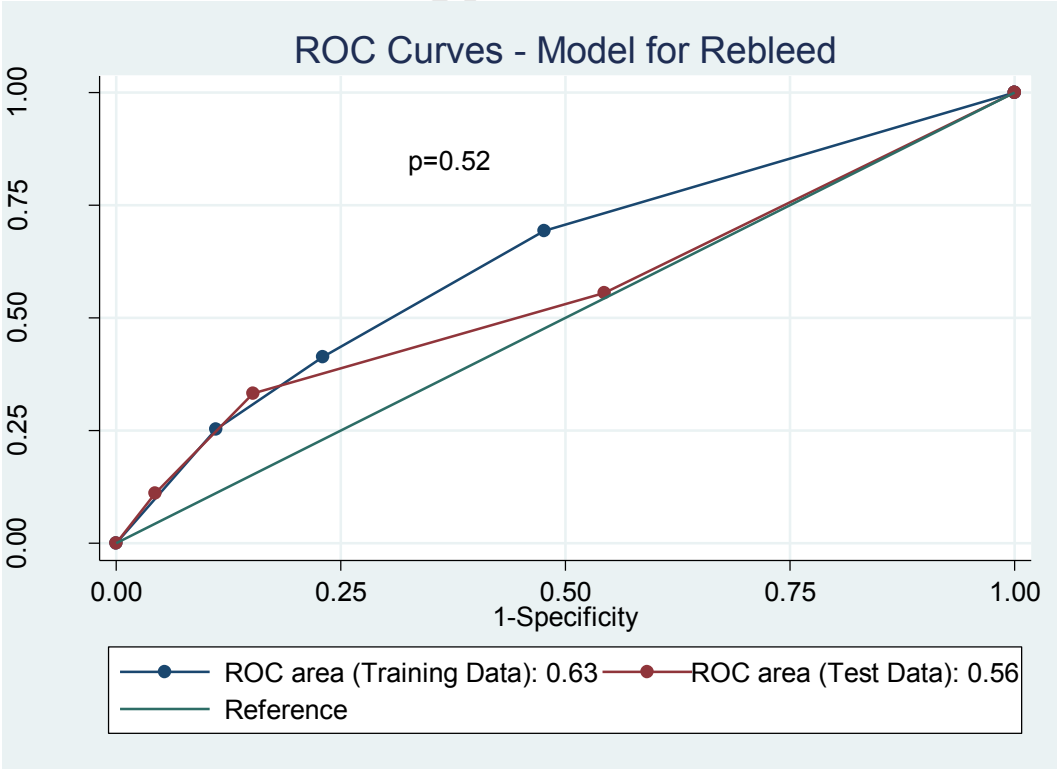
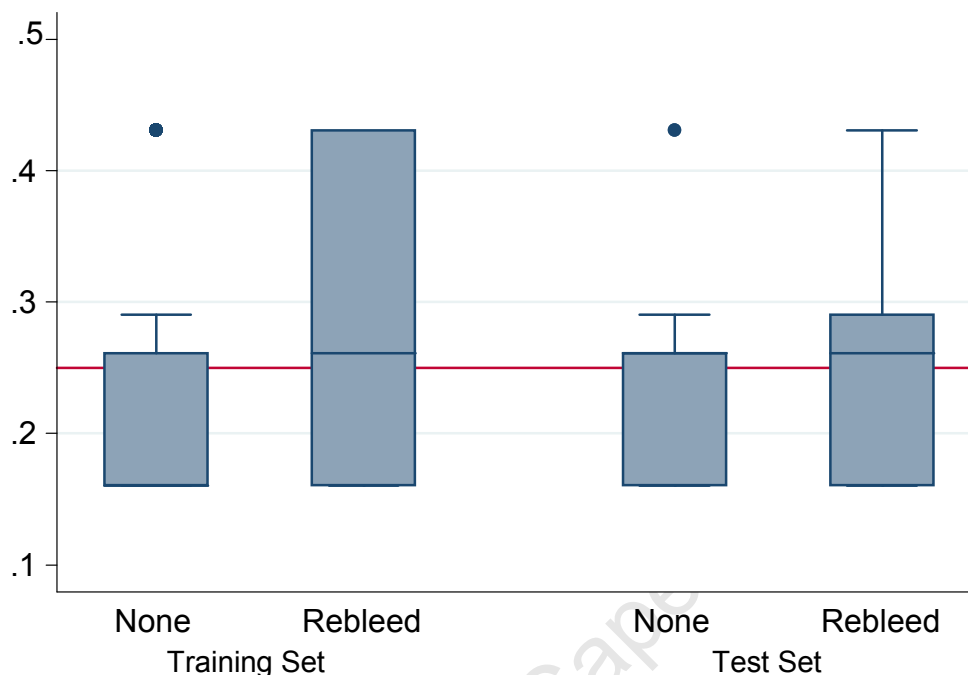


Figure 6.3 The ROC curves of the models generated with the Training and Test data for predicting variceal rebleeding within 6 weeks



**Figure 6.4** Box Plot of predicted probability for rebleeding



## DISCUSSION

This is the first study to examine risk factors for variceal rebleeding and death in an exclusively alcoholic cirrhotic population with acute bleeding oesophageal varices treated with emergency injection sclerotherapy. The study used data from easily obtainable clinical and biochemical information to identify risk factors which were validated in a subsequent patient sample. The risk factors included clinical (encephalopathy, ascites, balloon tube tamponade, >6 unit transfusion) and biochemical (bilirubin >51 mmol/L, INR >2.3, albumin <2.5mg/dL) data. As expected, most of the selected variables reflected the severity of the underlying liver disease and the magnitude of the bleeding episode (the need for a >6 unit blood transfusion or balloon tube tamponade). In this study inclusion was specifically

limited to alcoholic cirrhotic patients in order to have a clearly defined group and a uniform intervention in a population known to have a high rebleeding and mortality rate as more than 85% of the patients in this study were Child-Pugh grade B and C. The study demonstrated that although initial endoscopic intervention was effective in controlling initial acute variceal bleeding from oesophageal varices, one in four patients rebled during the first 6 weeks. The 6-week mortality rate in our cohort of decompensated alcohol-related cirrhotic patients was 24.8% which is similar to the 23.6% reported by D'Amico et al (D'Amico 2003) but higher than the 18.4% (Thomopoulos 2006), 17.5% (Chalasanani 2003), 15.3% (Boix 2007) and 14.5% (Carbonell 2004) mortality reported by other authors, a difference which may reflect the alcoholic population in our study.

Several previous studies have sought to identify prognostic indicators associated with early variceal rebleeding. In these studies multivariate analyses have demonstrated that active bleeding at emergency endoscopy (D'Amico 2003, Ben-Ari 1999, Siringo 1991, Zhao 2002, Jalan 2000), variceal size (Poynard 1987), Child-Pugh grade (D'Amico 2003, Thomopoulos 2006, Zhao 2002, Poynard 1987, Sanders 2002), Child Pugh score (Ben-Ari 1999, Siringo 1991, Bosch 2008, Bhasin 2004), hematocrit levels (D'Amico 2003, Bosch 2008), bacterial infection (Zhao 2002, Bosch 2008, Goulis 1998, Bernard 1999), encephalopathy (Ben-Ari 1999), portal vein thrombosis (D'Amico 2003), platelet count (Ben-Ari 1999), hepatocellular carcinoma (Poynard 1987, Bosch 2008), continued alcohol abuse (Ben-Ari 1999, Poynard 1987, Bosch 2008), hypoalbuminaemia (Zhao 2002) and a hepatic venous pressure gradient >20mm Hg (Bosch 2008, Avgerinos 2004, Monescillo 2004, Moitinho 1999) measured shortly after admission, have been reported as independent prognostic

factors for early rebleeding and significant predictors of risk for 5-day failure. The aggregate conclusions of these studies are however discordant and the predictive value of the combined results difficult to assess from the data (Krige 2009). Substantial differences in the studies include an absence of rigorous endoscopic criteria for defining variceal bleeding, a lack of standardisation of time of entry, and in patient sampling (percentage of alcoholics, percentage of Child-Pugh patients, active bleeding at endoscopy). Using multivariate regression analysis in the present study, two variables, bilirubin levels greater than 51 mmol/L and >6 units of blood transfused were significant predictors of rebleeding which is consistent with the reports of others (Ben-Ari 1999, Zhao 2002) and are markers reflecting the severity of the underlying liver disease and the magnitude of the bleeding episode.

There is a wide variation in the reported mortality rates after the first episode of variceal bleeding related in particular to differences in the interpretation of time 'zero' and the inclusion of patients beyond the first 48 hours of onset of initial bleeding. In addition some studies include patients who have had a first bleed as well as patients who present with subsequent variceal bleeds. In these selected groups mortality rates differ markedly. Published studies also include widely differing proportions of alcoholic and Child-Pugh grade C patients. (del Olmo 2000) The mortality rate in this study was 9.3% at 5 days and increased to 24.8% at 6 weeks. In an analysis of published data the most consistently reported predictive factors associated with an increased mortality at six weeks are active bleeding at endoscopy (de Franchis 2005), variceal size (Bosch 2003), hypovolaemic shock (Chalasani 2003, Thomopoulos 2006, de Franchis 2005), units of blood transfused (Le Moine 1992), early rebleeding (Thomopoulos 2006, Ben-Ari 1999, Graham 1981), the Child-Pugh

grade (Thomopoulos 2006, Sanders 2002, Bosch 2003, Graffeo 1994, Prindiville 1987, Yang 2007), MELD score >15 (Amitrano 2005), HVPG >20mmHg (de Franchis 2005), renal failure (de Franchis 2005, Cardenas 2001), blood urea or creatinine (Chalasanani 2003, Ben-Ari 1999, Bosch 2008, Garden 1985, Lata 2006, Gatta 1994), total bilirubin (Lata 2006, Gatta 1994, Hori 2006), INR (Le Moine 1992, Garden 1985, Lata 2006), ascites (Hori 2006), hepatic encephalopathy (Ben-Ari 1999, Le Moine 1992, Garden 1985, Srikureja 2005), albumin (Prindiville 1987, Lo 2004), bacterial infection (Yang 2007) and hepatocellular carcinoma (Bosch 2008, de Franchis 2005, Amitrano 2005, Gatta 1994, Hori 2006), continued alcohol abuse (Bosch 2008) and age (Carbonell 2004) has been previously reported. We used univariate and multiple logistic regression analyses to determine which variables were most predictive of 6 week mortality. The key finding in our study was the identification in the final multivariate regression analysis model of 6 independent prognostic factors for overall survival at 6 weeks.

Several studies have evaluated the clinical factors associated with early mortality after endoscopic intervention for acute variceal bleeding. Previous investigators have shown that the severity of the bleeding episode (shock on admission to the hospital) and the Child-Pugh grade (Thomopoulos 2006) are independent predictors of short-term mortality while others have reported that a Child-Pugh score of >9, orthostatic hypotension, systolic blood pressure <100mmHg, diastolic pressure of <60mmHg, failure to control bleeding, placement of a Minnesota tube, airway intubation, transfusion requirement >5 units, and aspiration pneumonia were associated with an increased in-hospital mortality (Chalasanani 2003, Bhasin 2004). In a retrospective study of 124 cirrhotic patients with variceal bleeding, Le Moine et al found that of 24

variables studied, encephalopathy, prothrombin time and the number of blood units transfused within 72 hours had independent prognostic value (Le Moine 1992). Gatta et al found that s-creatinine, ascites on admission, diagnosis of hepatocellular carcinoma and prothrombin index were the best set of significant predictor co-variates (Gatta 1994). Other investigators have shown that the severity of bleeding as assessed by shock on admission to the hospital and the Child-Pugh grade (Thomopoulos 2006) are independent predictors of short-term mortality while others have reported that a Child-Pugh score of >9, orthostatic hypotension, systolic blood pressure <100mmHg, diastolic pressure of <60mmHg, failure to control bleeding, placement of a Minnesota tube, airway intubation, transfusion requirement >5 units, and aspiration pneumonia were associated with an increased in-hospital mortality (Chalasanani 2003, Bhasin 2004).

Although several prognostic models have been proposed to predict mortality in patients with cirrhosis (Chalasanani 2003, Thomopoulos 2006, Bhasin 2004, Le Moine 1992, Garden 1985, Gatta 1994), the Child-Pugh score remains the most widely used scoring system both in clinical practice and in clinical research (D'Amico 2006) and is superior to any other predictive factor in determining mortality within the first six weeks after a major variceal bleed (Jalan 2000, Garcia-Tsao 2008, Atkinson 2008, Sanders 2002, Angermayr 2003). In a systematic review of 118 studies of cirrhotic patients, the most common independent predictor of death was the overall Child-Pugh score, followed by each of the five components of the Child Pugh score (D'Amico 2006). The advantages of the Child-Pugh (C-P) score over other more complex scores such as the Model for End-Stage Liver Disease (MELD) score, is that the C-P score is simple and easy to use and can be calculated at the bed-side

using mental arithmetic. Two significant flaws in the Child-Pugh score, however, are the subjectivity in the assessment of the degree of ascites and encephalopathy and the inability to distinguish mild from severe grade C patients with sufficient discrimination (Cholongitas 2005). In a comparative study testing the ability of MELD and CTP scores in predicting mortality following acute variceal bleeding in 239 cirrhotic patients, Chalasani et al found that MELD was not superior to the commonly used C-P score (Chalasani 2003). These authors stress that calculating the MELD score is complex while the C-P system is well established, its components are easily obtained and is easy to calculate at the bedside (Chalasani 2003). In 3 studies by Bambha (Bambha 2008), Chalasani (Chalasani 2003), and Amitrano (Amitrano 2005) MELD was a clinically useful and objective predictor of short-term survival after AVH. Prognostic scoring in acute variceal bleeding continues to evolve and updated versions of the original C-P and MELD scores are now available (Huo 2008). The C-P grade and scores in our study showed significant discrimination between grade A, B, and C patients and the incidence of rebleeding and death at 6 weeks. In our study, each of the individual components of the C-P classification correlated with survival using multivariate analysis and was validated in the test group, independently confirming the accuracy of the C-P grading classification.

The proposed risk predictor models generated in this study were shown to be valid and predictive. The concordance (c)-statistic showed that the predictive models had values between 0.83 and 0.87 indicating excellent predictive accuracy. As in previous studies (D'Amico 2003) prognostic indicators of 6 week mortality were related predominantly to the degree of liver decompensation rather than the severity of variceal bleeding. As expected, the majority of selected co-variates were related

to the severity of underlying liver disease. The multivariate analysis selected each of the components of the Child-Pugh grade, emphasizing the inherent value of the Child-Pugh system. In addition our study showed that balloon tamponade and >6 units of blood reflected the magnitude of the variceal bleed. The concordance statistic was less good for the prediction of rebleeding, suggesting that additional factors, other than liver function, such as variceal size or portal pressure, may be responsible for variceal rebleeding.

A major strength of this study is that it was conducted in a single centre in a well defined population of consecutive patients using a standard endoscopic injection technique and was supervised by the same group of investigators during the study period. All included patients were at a well defined stage in the course of cirrhosis (inception cohort) thereby homogenising the study population and avoiding the error of overfitting which has influenced a significant proportion of previous studies (D'Amico 2006). In order to provide the highest possible level of uniformity and to minimise differences in the zero-time entry, only patients who received their initial and subsequent treatment in our unit were studied. The robustness of this study is enhanced by the prospective data collection, restriction of subjects to alcoholic cirrhotics and the complete follow-up of the cohort. The use of rebleeding and death as the main outcomes provided consistent and objective end-points in the study. Unlike other studies which included non-consecutive patients, incomplete reporting of inclusion and exclusion criteria and have incomplete follow-up or inclusion of patients at differing disease stages without separate analyses, our study design avoided these pitfalls by excluding non-measurable biases.

This study has several important limitations. The study did not test all the previously reported risk factors for variceal rebleeding and death in the univariate and multivariate analysis as this study was a retrospective analysis of prospectively documented data. Future prospective studies evaluating the full spectrum of proposed risk factors from other centres will be necessary to provide the definitive risk equation. Although the technique of sclerotherapy remained constant, this study assessed patients over a 26 year period during which improvements in supportive care, vasoactive drugs and antibiotic therapy have occurred. In this study prophylactic antibiotics were given initially only to patients with ascites to prevent spontaneous bacterial peritonitis. In the light of compelling new data, antibiotics are now given to all patients with acute variceal bleeding (Thalheimer 2005). Endoscopic banding has now replaced injection sclerotherapy in most units, although a recent meta-analysis concludes that banding and sclerotherapy are equally effective for acute variceal bleeding (Triantos 2006).

Despite the development of several scoring systems for risk stratification in patients with portal hypertension and bleeding oesophageal varices, only the Child-Pugh classification and more recently, the MELD score, have universal appeal. This lack of integration into clinical practice of the new systems may be due to insufficient validation, complex formulae with cumbersome calculations for daily bed-side use, limited clinical applicability, or inability to identify patients with significant but non GI comorbidity (Imperiale 2007).

Despite substantial improvement over the past two decades in the overall survival after variceal bleeding, the 6 week mortality remains discouragingly high, especially in Child-Pugh grade C patients (Thabut 2007). Patients die from uncontrolled bleeding, early rebleeding, infection, liver and renal failure in the first weeks after a bleeding episode. Factors independently associated a higher mortality are poor liver function, severe portal hypertension with a HVPg > 20 mmHg and active bleeding at endoscopy. The essential requirements necessary to improve survival are effective control of acute variceal bleeding, prevention of further rebleeding and minimising deterioration of liver function.

Identification and knowledge of accurate prognostic data predicting early rebleeding can ideally provide a powerful tool to identify at an early stage those patients in whom conventional treatment is likely to be unsuccessful and who require urgent implementation of an aggressive salvage strategy or identify those with a very poor prognosis in whom chances of survival are slim. In this study risk factors to predict early rebleeding and death in alcoholic cirrhotic patients with variceal bleeding were calculated from easily obtained clinical, biochemical and endoscopic data and was validated in an independent sample. Future prospective studies incorporating and evaluating the full spectrum of prognostic factors including clinical variables, renal function and liver biochemistry, endoscopic intervention, portal pressures and validation of the new scoring systems will be a valuable addition to improving the effective management of patients with bleeding oesophageal varices and portal hypertension.

## CHAPTER 7:

### SUMMARY AND CONCLUSIONS

#### Study 1

The first study in this thesis evaluated the incidence of variceal eradication, variceal recurrence and rebleeding and death in a large cohort of patients with alcohol-induced cirrhosis and bleeding varices treated with serial endoscopic variceal injection sclerotherapy. The study sought to determine accurate long term survival data in alcoholic patients with cirrhosis who had bled from oesophageal varices and tested the validity of the hypothesis that eradication of oesophageal varices by repeated injection sclerotherapy would reduce recurrent variceal bleeding and death from bleeding varices.

The study evaluated 287 consecutive alcoholic cirrhotic patients who presented with acute oesophageal variceal bleeding and underwent a total of 2565 upper gastrointestinal endoscopic sessions which included 353 emergency and 1015 elective variceal injection treatments during the study period. Rebleeding after the index injection sclerotherapy procedure occurred in 104 of the 287 (36.2%) patients before eradication. These 104 patients had a total of 170 bleeds during 164 subsequent admissions before the varices were eradicated. Ninety one patients bled from varices and 13 patients bled from non-variceal sources. The 91 patients had 124 variceal bleeds which were successfully treated with acute emergency injection sclerotherapy on 113 occasions.

Eradication and subsequent recurrence of oesophageal varices after sclerotherapy was assessed in 182 of the 287 patients who survived and who were followed up for

more than 3 months. Oesophageal varices were eradicated in 147 of the 182 patients (80.7%) after a median of 5 injections (range: 1 to 14). Mean survival in these 147 patients was 47.1 months (median 36.8 months) with the mean survival in Child-Pugh grades A, B and C of 40.2, 37.4 and 24.0 months. Oesophageal varices remained eradicated in 69 patients (mean follow-up from eradication: 34.6 months, median 23.6 months; range 1 to 174). Mean survival in these 69 patients in whom varices remained eradicated was 39.6 months (median 31.7 months). Forty five of the 78 (57.7%) patients with recurrence of oesophageal varices after eradication presented with variceal bleeding after a mean of 16 months (range: 0.5 to 172 months).

Minor complications of sclerotherapy were common after acute injection for active bleeding and included dysphagia, transient fever and pulmonary atelectasis. A total of 747 complication events were documented in 234 patients during surveillance or unscheduled follow-up endoscopy after a prior variceal injection. Mucosal ulceration at the injection site was found at follow-up endoscopy on 531 occasions in 199 patients. An oesophageal stricture at the injection site occurred in 25 patients after sclerotherapy, 9 of whom required oesophageal dilatation on 29 occasions with relief of symptoms. Two patients developed an intramural oesophageal haematoma after sclerotherapy which resolved on conservative therapy. Perforation of the oesophagus occurred in 8 patients as a consequence of repeated sclerotherapy to control of recurrent acute variceal bleeding. Five of these 8 patients survived, including 3 who required surgery to treat the complication.

Cumulative survival of the 287 patients by life table analysis was 67% at 1 year, 42% at 3 years, 26% at 5 years and 13% at 10 years. Survival according to Child-Pugh grade A was 68% at 3 years, 48% at 5 years and 37% at 10 years. Survival of Child-Pugh grade B patients at 3 years was 54%, 34% at 5 years and 17% at 10 years, and survival of Child-Pugh grade C patients was 21% at 3 years, 13% at 5 years and 7% at 10 years. Two hundred and one (70%) of the 287 patients died during the course of the study. Liver failure was the commonest cause of death and occurred in 113 patients. Hepatorenal failure was the cause of death in 23 patients. Twelve patients died of pneumonia, 37 of multi-organ failure, often precipitated by bleeding varices and 3 died of bleeding from other sites.

Ultimate survival and outcome of treatment in this consecutive cohort of patients was disappointing. Although varices were eradicated in 82% of patients who survived more than 3 months, recurrent varices ultimately developed in 57% of patients, half of whom had further variceal bleeding. Several important and unresolved problems related to the role of repeated sclerotherapy in the long-term management of patients with oesophageal varices remain. There is increasing recognition that an important limitation of long-term sclerotherapy is the substantial incidence of rebleeding which is a particular feature of the early phase after endoscopic therapy has begun. The most common source of recurrent bleeding before variceal eradication in this study was from patent residual varices which occurred in one third of our patients. Urgent repeat endoscopy is essential since in most patients with recurrent bleeding, varices were the source and were effectively treated by sclerotherapy. Serial sclerotherapy successfully eradicated oesophageal varices in 80% of the patients in this study. Although new varices formed following initial

obliteration in 53% of patients, this was associated with rebleeding in only 30% which would support the validity of the concept of variceal eradication as a specific endpoint of treatment.

While the risk of rebleeding diminishes with time as the variceal channels are obliterated, some recurrent bleeds are major and may contribute to deaths from liver failure. Any protocol for long-term endoscopic management of variceal haemorrhage requires a firm definition of treatment failure which allows alternative treatment options to be instigated. That such a definition is difficult to formulate, is reflected in the major discrepancies in the proportion of treatment failures in the larger controlled trials. There is consensus that patients who have life-threatening variceal bleeding after an adequate course of endoscopic treatment should be regarded as failures of long-term treatment and in this cohort a TIPS shunt gives the best results. Other logistic problems related to long-term sclerotherapy include the need for lifelong follow-up with repeated injections because most varices ultimately recur in time. Surviving patients place an increasing burden on hospital resources, even when sclerotherapy is performed on an outpatient basis.

The long term data in this study has documented the variceal recurrence and rebleeding rate using a standard sclerotherapy technique. No comparable data exist for variceal ligation and ligation will require similar long term data to validate and vindicate its current status as the preferred endoscopic technique. Our current management policy is for patients to have regular endoscopic therapy in order to achieve early variceal eradication, appreciating that factors such as oesophageal ulceration and poor patient compliance may interfere with the endoscopic therapy

programme. After eradication of the varices, patients have surveillance endoscopy at six and then 12 month intervals and, if recurrent varices are identified, a comprehensive endoscopic treatment schedule is instituted again. Ultimately the use of sequential combined endoscopic techniques with variceal banding initially when varices are large followed by sclerotherapy when varices are small may enhance the endoscopic management of oesophageal varices both in terms of reducing complications, facilitating earlier eradication and preventing recurrence.

### **Study 2**

The second study demonstrated that endoscopic therapy was highly effective in controlling acute bleeding from oesophageal varices and that ultimate survival was influenced by both rebleeding and underlying liver reserve. Sustained control of acute bleeding has been shown to be a critical requirement in variceal management because each subsequent bleed worsens marginal liver function. Although initial endoscopic intervention controlled acute variceal bleeding in 304 of the 310 patients, one quarter of the patients rebled during the first 6 weeks. There were no deaths in Child-Pugh grade A patients and in this cohort with preserved liver function, early mortality was not influenced by the severity of the bleeding episode. Our data demonstrated that Child-Pugh grade C patients, who have the least hepatic reserve, were more likely to have a major bleed and require pitressin or octreotide and balloon tamponade in addition to sclerotherapy to control acute bleeding. The study showed that in this high risk group, even when sclerotherapy successfully controlled variceal bleeding, progressive liver failure resulted in high mortality rates in the first 6 weeks after admission, especially in Child-Pugh patients scoring >13 with an 80% mortality.

The results of this study clearly defined the course and prognosis of patients with decompensated alcohol-related cirrhosis and bleeding varices. Despite substantial improvement in overall survival in recent years, the 6 week mortality after variceal bleeding remains discouragingly high, especially in Child-Pugh grade C patients who succumb either from uncontrolled initial variceal bleeding or early rebleeding, or subsequently from the consequences of infection, liver and renal failure in the first weeks after a bleeding episode. As shown in this study, most deaths were due not to bleeding, but to the detrimental systemic consequences which lead to progressive deterioration of liver function. The presence of advanced Child-Pugh score  $>13$  in this study identified those patients at higher risk of mortality. Our study confirms the observations of others that in experienced centres endoscopic injection sclerotherapy can be performed safely and effectively in alcoholic cirrhotic patients with actively bleeding oesophageal varices. However, even under optimal conditions, currently available treatment options fail to control initial variceal bleeding or prevent early rebleeding in up to 20% of patients some of whom may require rescue intervention. Because most patients who fail first line endoscopic and pharmacological therapy are high risk and have marked liver decompensation complicating the variceal bleeding, early recognition of endoscopic failures and implementation of salvage procedures should provide better haemostasis in this cohort.

### **Study 3**

The third study is the first detailed evaluation and analysis to examine risk factors for rebleeding and death in an exclusively alcoholic cirrhotic population treated with endoscopic injection sclerotherapy. The study used data from easily obtainable

clinical and biochemical information to identify risk factors which were validated in a subsequent sample. The risk factors included clinical (encephalopathy, ascites, balloon tube tamponade, >6 unit transfusion) and biochemical (bilirubin >51 mmol/L, INR >2.3, albumin <2.5mg/dL) data. As expected, most of the selected variables reflected the severity of the underlying liver disease and the magnitude of the bleeding episode. Inclusion was specifically limited to alcoholic cirrhotic patients in order to have a clearly defined group and a uniform intervention in a population known to have a high rebleeding and mortality rate as more than 85% of the patients in this study were Child-Pugh grade B and C. Univariate analysis was used to determine the unadjusted risk factors for rebleeding and death. When predictors of rebleeding during the first 6 weeks were considered, logistic regression analysis found that >6 units of blood transfused, the presence of ascites and a bilirubin level >51 mmol/L were the best set of significant predictor covariates. However, in the final stepwise multivariate logistic regression analysis model, only two variables, bilirubin levels greater than 51 mmol/L and >6 units of blood transfused during the initial hospital admission were significant predictors of rebleeding.

Univariate logistic regression analysis found that >6 unit blood transfusion, pitressin or octreotide infusion, the presence of encephalopathy and ascites, the need for a balloon tube to control acute bleeding, a prolonged INR >2.3, a low serum albumin of level <2.5mg/dL, and increased bilirubin levels >51 mmol/L were significant predictors of death at 6 weeks after the initial variceal bleed. In the final multivariate logistic regression analysis model, six variables, encephalopathy, ascites, bilirubin levels >51 mmol/L, a prolonged INR >2.3, an albumin level <2.5mg/dL and the need

for balloon tube tamponade were significant predictors of death within the first 6 weeks.

The validity of the models identified in the multivariate analyses for rebleeding and death at 6 weeks in the 310 study patients (“the training set”) were tested against a subsequently treated group of alcoholic cirrhotic patients with endoscopically proven bleeding oesophageal varices who had endoscopic control of bleeding in the unit (“the test set”). The area under the receiver operating characteristic curve for each model in the test set was not significantly different from the corresponding area in the training set, indicating that the predictive sensitivity and specificity observed in the training set were accurately reproduced in the test set. The concordance (c)-statistic yielded values in the model for death ranged from 0.84 to 0.87, indicating a robust model with good predictive accuracy. The calculated threshold for death in the box plot was 30% with the proposed model accurately predicting a high risk of dying in those patients above the 30% threshold. The concordance(c)-statistic in the model for rebleeding at 6 weeks was less predictive with values ranging from 0.56 to 0.63 indicating that the selected variables in the proposed model for variceal rebleeding at 6 weeks were less likely to identify those patients who might rebleed than those likely to die. Similarly, the box plot indicated that the proposed model for rebleeding was less accurate at predicting those patients who were likely to rebleed within the 6 week period, suggesting that the candidate variables selected by uni- and multivariate analyses, which mainly represented liver function, were more accurate in predicting survival or death which is a function of liver reserve than predicting rebleeding which may be related or dependent on additional unrecognised or untested factors. These validated risk factors may be of value in identifying patients

on admission who may not benefit from standard treatment alone and to stratify patients in future controlled trials.

### **Recommendations regarding the technical aspects of sclerotherapy**

Endoscopic therapy is an established and integral part of the management of acute variceal bleeding and the long-term treatment of patients after a variceal bleed. Although complications after endoscopic therapy for variceal bleeding are common, most are minor and do not interrupt the treatment programme. In a small group of patients however, the success of therapy is compromised by recurrent bleeding and serious procedure-related complications. Most of the serious complications related to endoscopic therapy occur in patients with severe liver disease in whom control of bleeding is difficult. Mature clinical judgment is necessary in acute problematic or complex cases and careful supervision of trainees or assistance by an experienced endoscopist becomes essential when critical decisions are required. Early and close multidisciplinary consultation is often useful in demanding cases to facilitate appropriate therapy and optimal management.

Injection sclerotherapy is an invasive endoscopic procedure which requires a high level of manipulative skill and mature judgement. Complications related to injection occur mostly during acute major or recurrent bleeding when varices are large and the patient is restless or unco-operative. The incidence of complications varies widely in reported studies because of variations in patient population, the type and severity of the underlying liver disease and the different injection techniques used.

A number of critical generic technical and procedural precautions are important to avoid both local and systemic complications, regardless of the type or technique of endoscopic intervention used to control acute bleeding. Effective resuscitation must precede endoscopy in patients with evidence of recent major bleeding. Diagnostic and therapeutic endoscopy should be performed in a well equipped unit with competent assistance and careful monitoring. Early endotracheal intubation is crucial if major bleeding occurs. Precise and accurately placed injections are essential. Uncontrolled blind, large volume injections during active bleeding must be avoided. The sclerotherapy needle should not exceed 5mm in length and a short bevel reduces the risk of deep injections and extravasation of sclerosant and injury to the underlying oesophagus. Recurrent bleeding after injection sclerotherapy requires careful evaluation and repeat endoscopy to determine the source. If variceal bleeding continues or recurs during the index admission despite 2 adequate injections, other definitive therapy should be instituted.

Variceal eradication with band ligation requires fewer endoscopic treatment sessions, and causes substantially less oesophageal complications. Although the incidence of early gastrointestinal rebleeding is reduced by band ligation in most studies, this does not result in an overall survival benefit relative to injection sclerotherapy. Simultaneous combination therapy band ligation plus injection sclerotherapy of large varices confers no advantage over band ligation alone. A staged approach with initial band ligation followed by injection sclerotherapy when varices are small requires further evaluation as the sequential combination may prove to be the optimal method of minimizing variceal recurrence. Overall, current data demonstrate clear advantages for using band ligation in preference to injection

sclerotherapy. Band ligation should therefore be regarded as the endoscopic technique of choice in the treatment of oesophageal varices.

The range of treatment options for bleeding oesophageal varices has expanded markedly during the past three decades with a substantial reduction in mortality to current levels of around 20%. This significant overall improvement in survival reflects the progress in both the general management of severely ill cirrhotic patients and treatment of hepatic decompensation which strongly influence the prognosis. Optimal management should provide the full spectrum of treatment options which include pharmacological therapy, endoscopic treatment, interventional radiological procedures, surgical shunts and liver transplantation. The treatment of acute bleeding and prevention of recurrent variceal bleeding is best accomplished by a skilled, knowledgeable, and well equipped team using a multidisciplinary integrated approach.

### **Assessment and recommendations for future research**

This review has shown considerable variation in the quality of randomised trials in cirrhotic portal hypertension, especially with regard the generation of allocation sequence and allocation concealment which may raise the risk of selection, assessment and attrition bias. Despite the plethora of randomised controlled trials in portal hypertensive bleeding, these deficiencies leave unanswered questions. Understanding the problems inherent in the design, execution and interpretation of clinical trials in portal hypertension is critical in deciding whether the results apply to the care of a specific patient. For example, when assessing endoscopic control of bleeding and survival in patients with varices, trials with a large proportion of

alcoholic patients who have advanced cirrhosis and liver decompensation are less likely to show a difference in bleeding control as death from recurrent bleeding is replaced by early death from liver failure in a high risk population.

The statistical power of trials remains a major problem in portal hypertension trials, where modest survival advantages are unlikely to be detected unless large-scale, multicentre randomised trials are undertaken incorporating sufficient patient numbers. Very few of the published trials have performed blinded outcome assessment. Better understanding of the principles involved in the design and implementation of clinical trials and analysis of data will increase the number of high quality of randomised controlled trials which may resolve some of the issues. There is a need to use standardised definitions for the critical end points in portal hypertension and bleeding varices e.g. control of bleeding, rebleeding and treatment failures. Issues of quality of life and cost effectiveness are becoming increasingly important concepts to include in trial design.

The implications for future research into portal hypertension are that adequately powered, adequately conducted, properly reported multicentre trials need to continue to address unresolved issues. As patient recruitment becomes an increasing impediment, future study conduct require internationally accepted standard protocols to facilitate aggregate analyses and future meta-analyses. In addition, the ever increasing demand for medical fiscal discipline and logistic efficiency require the issue of cost to be adequately addressed in prospective studies. These issues have been raised at the Baveno Consensus Conferences.

Identification and knowledge of accurate prognostic predicting early rebleeding should ideally provide a powerful tool to identify at an early stage those patients in whom conventional treatment is likely to be unsuccessful and who require urgent implementation of an aggressive salvage strategy. Future prospective studies incorporating and evaluating the full spectrum of prognostic factors including clinical variables, liver biochemistry, endoscopy and portal pressures and comparative MELD and Child-Pugh assessment will be valuable advances in improving the effective and rational management of patients with bleeding oesophageal varices and portal hypertension.

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