SURVIVAL IN HEPATITIS-B CIRRHOSIS COMPARED TO ALCOHOLIC CIRRHOSIS IN PATIENTS WITH CHILD'S C LIVER DISEASE: A PROSPECTIVE STUDY OF ENDOSCOPIC SCLEROTHERAPY FOR BLEEDING OESOPHAGEAL VARICES

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ABSTRACT

A prospective comparative study was carried out on thirty-seven consecutive patients presenting with bleeding oesophageal varices at University Hospital, Kuala Lumpur. All patients received injection sclerotherapy if active bleeding was seen at the time of initial endoscopy, followed by repetitive courses of sclerotherapy to obliterate the varices. Predominant aetiological factors were hepatitis-B cirrhosis (43%) and alcoholic cirrhosis (30%). Chinese ethnic group accounted for 62.5% of hepatitis-B cirrhotics and Indian 73% of alcoholic cirrhotics. After excluding patients lost to follow-up, analysis of the remaining thirty-four patients showed reduced long-term survival in patients with Child's C disease. Log-rank analysis of survival curves between hepatitis-B cirrhosis and alcoholic cirrhosis in patients with Child's C liver disease showed no significant difference in long-term survival (p=0.07). However, six deaths were seen in hepatitis-B cirrhosis compared to one death in alcoholic cirrhosis in the first eight months of follow-up. Most patients died from progressive liver failure. Median survival for Child's C hepatitis-B cirrhosis was 7.5 months whereas this had not been reached for Child's C alcoholic cirrhosis (median follow-up 11.6 months). We conclude that variceal haemorrhage in Child's C hepatitis-B cirrhosis is a bad prognostic sign and is associated with reduced survival with a median survival of 7.5 months despite control of the variceal bleed.

Keywords: *varices, sclerotherapy, hepatitis-B, alcoholic cirrhosis.*

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INTRODUCTION

Haemorrhage from oesophageal varices is a life-threatening event in cirrhotic patients. Among patients admitted for first variceal bleed, rebleeding will occur in 70%[1] and mortality was 42% at six weeks after hospitalisation[2]. Standard medical or surgical therapy has included fluid and blood replacement, vasopressin infusion and balloon tamponade but is often followed by repeated episodes of haemorrhage and has little effect on survival[1]. Porta-caval shunting stops the bleeding but at the expense of increased risk of encephalopathy and no overall improvement in survival regardless of the type of shunt[1].

Recently injection sclerotherapy has replaced shunt surgery as the first line treatment for initial haemostasis of variceal haemorrhage[1] and most studies indicate that sclerotherapy is superior to medical management when results are measured by the control of active bleeding and the prevention of recurrences[3-8], and a meta-analysis of seven trials showed that overall survival was improved by this treatment[9,10]. Sclerotherapy also appears to be equal or superior to portacaval or selective splenorenal shunt in terms of both survival and the preservation of cerebral function[11-13]. In contrast to shunt surgery, it does not preclude transplant surgery at a future date.

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Since most of the major trials so far reported had cryptogenic and alcoholic cirrhosis as the major aetiological factors and little reference was made to hepatitis-B cirrhosis, we decided to investigate the role of sclerotherapy in hepatitis-B cirrhosis in comparison to alcoholic cirrhosis after a variceal bleed. The preliminary findings are presented.

PATIENTS AND METHODS

Thirty-seven consecutive patients presented to University Hospital, Kuala Lumpur, with variceal haemorrhage, confirmed by endoscopy were followed up prospectively and analysed for aetiological factors, rebleeding incidence and survival. Patients with underlying hepatoma were excluded from the study. Three patients were excluded from the final analysis because of loss of follow-up after control of the initial variceal bleed.

Management of the presenting bleed and any subsequent rebleeding was initially with blood transfusion, together with balloon tamponade and vasopressin if bleeding did not stop spontaneously. Sclerotherapy was carried out as soon as possible and this varied between one hour to two days. All injections and follow-up endoscopy were performed by a single endoscopist. Intravenous diazepam 10 mg was used for sedation and sclerotherapy was performed using an Olympus flexible GIF Q10 or K2 endoscope and a flexible Olympus needle injector. Sodium tetradecyl sulfate was injected directly into each visible varix at or just proximal to the gastro-oesophageal junction. Sclerotherapy was repeated every week until the oesophageal varices became insignificant or too small to be injected. Thereafter, endoscopy was done at 3-6 monthly interval and the varices injected if they recurred.

On admission, the underlying severity of liver disease was graded A, B or C accordingly to a modification of Child's classification[14]. Serologic investigations for hepatitis B virus (hepatitis B surface antigen and hepatitis Be antigen) and alpha-feto protein were conducted in all subjects. Patients were

considered to have cirrhosis on the basis of liver biopsy or imaging procedures (computed tomography, ultrasonography or isotope-liver scan) and clinical and biochemical findings. Hepatitis-B was considered as the aetiology of cirrhosis if hepatitis-B surface antigen was present in the patient's serum and likewise alcoholic cirrhosis was diagnosed if the patient admitted drinking more than 50 gram daily or if there was corroboration from relatives and if the histological appearances were compatible.

Rebleeding was defined as bleeding with haematamesis and/or melaena and endoscopy showed the most likely source of bleeding was from the varices itself or secondary to sclerotherapy-induced ulcer. Peptic ulcer is excluded as a cause of rebleeding.

Statistical analyses were performed using chi-square with Yate's correction, Fisher's exact test and Log-rank test for comparison of the survival curves. Cumulative survival curves were plotted according to Peto et al[15]. Survival was calculated from the first episode of variceal haemorrhage. Significance was accepted at $p<0.05$.

RESULTS

Patient characteristics are summarised in Table I. The median age of all patients was 53 years (range 30-76). Predominant aetiological factors were hepatitis-B cirrhosis (43%) followed by alcoholic cirrhosis (30%). Chinese ethnic group accounted for 62.5% of hepatitis-B cirrhosis and Indian 73% of alcoholic cirrhosis. The majority of the patients had Child's C cirrhosis (62%). All the patients except two had their initial variceal haemorrhage and subsequent rebleeding successfully controlled with the measures outlined above. At the time of first endoscopic sclerotherapy, active bleeding evidenced by fresh blood or oozing of blood from the varices were seen in 19 patients. Successful obliteration of oesophageal varices was achieved in 29 patients (85%). The mean number of injection courses for obliteration of oesophageal varices was 4.24 (range 2-8) sessions.

Table I – Patient Characteristics

Total no. of patients	37
Median age in years (range)	53 (30-76)
Sex (M/F)	26/11
Aetiology:	
Hepatitis-B cirrhosis	16 (43 %)
Alcoholic cirrhosis	11 (30 %)
Cryptogenic cirrhosis	9 (24.5%)
Idiopathic portal hypertension	1 (2.5%)
Child's classification (modified)	
Grade A	7 (19 %)
Grade B	7 (19 %)
Grade C	23 (62 %)

Rebleeding

During the median period follow-up of 11.6 months (range 1.9-22) in 34 patients, rebleeding occurred in 18 patients (53 percent), and in 16 patients rebleeding occurred before obliteration of the varices. It is therefore important to continue sclerotherapy until the varices are obliterated. Rebleeding was seen more frequently in Child's C patients (67%) compared to Child's A (28%) and Child's B patients (33%), the difference, however, was not significant [C vs (A+B), $x^2=2.84$, $p=0.09$] (Table II). Comparison of the rebleeding incidence between hepatitis-B cirrhosis and alcoholic cirrhosis also showed no significant difference (Table III). Rebleeding was controlled except in two patients. One died from uncontrolled variceal bleeding from gastric varices 13 months after first sclerotherapy and the second patient died from recurrent bleeding from sclerotherapy-induced oesophageal ulcer 2 weeks after initial sclerotherapy.

Table II – Rebleeding after initial sclerotherapy according to Child's classification

	Child's Class A	B	C	Total
No. of patient with rebleeding*	2/7 (28%)	2/6 (33%)	14/21 (67%)	18/34 (53%)
No. of rebleeding episodes	3/28 (11%)	2/28 (7%)	23/28 (82%)	28/28 (100%)

* C vs (A+B) : $x^2 = 2.84$, $p = 0.09$

Table III – Comparison of Hepatitis-B and alcoholic patients

	Hepatitis-B (n = 14)	Alcoholic (n = 10)	p value
Mean age (years)	52.6	47.7	–
Sex (M:F)	11:3	10:0	–
Child's class			
Grade A	2 (14%)	3 (30%)	–
Grade B	3 (21%)	0 (0%)	–
Grade C	9 (64%)	7 (70%)	–
Rebleeding (no of patients)	7 (50%)	5 (50%)	n.s.
Deaths in first 6 months	4 (29%)	0 (0%)	–
*Total no of deaths (Child's C patients)	6 (43%)	1 (10%)	p = 0.077

n.s. = not significant
*see Fig 2, log-rank test of survival curves.

Mortality

The overall mortality was 29% (10/34) and exclusively confined to Child's C cirrhotic patients. Survival was significantly worse for Child's C patients compared to Child's A and B patients (Fisher's exact test; C vs A+B: $p = 0.002$), (Table IV). There were 10 deaths and 7 were attributed to progressive liver failure. The remaining 3 deaths were due to bleeding gastric varices, bleeding oesophageal ulcer induced by sclerotherapy and respiratory failure due to massive pleural effusion. Out of the 10 deaths, 6 occurred in the hepatitis-B group, 2 in cryptogenic cirrhosis, one each in alcoholic and idiopathic portal hypertension. Comparison of survival curves between hepatitis-B cirrhosis and alcoholic cirrhosis using log-rank tests showed no significant difference ($p=0.20$, see Fig 1) but there were more early deaths in the hepatitis-B group compared to the alcoholic group (4 compared to none in the first 6 months after a first bleed, see Table III). Comparison of survival curves between hepatitis-B cirrhotics and alcoholic cirrhotics in patients with Child's C liver disease showed reduced survival approaching significant value (Log-rank test; $p=0.07$, see Fig 2) in hepatitis-B cirrhosis. The median survival for Child's C hepatitis-B cirrhosis was 7.5 months whereas this has not been reached for Child's C alcoholic cirrhosis during our study. All deaths except one in the hepatitis-B cirrhosis group were attributed to progressive liver failure.

Fig 1 – Survival of patients with hepatitis-B cirrhosis and alcoholic cirrhosis treated with injection sclerotherapy following bleeding varices

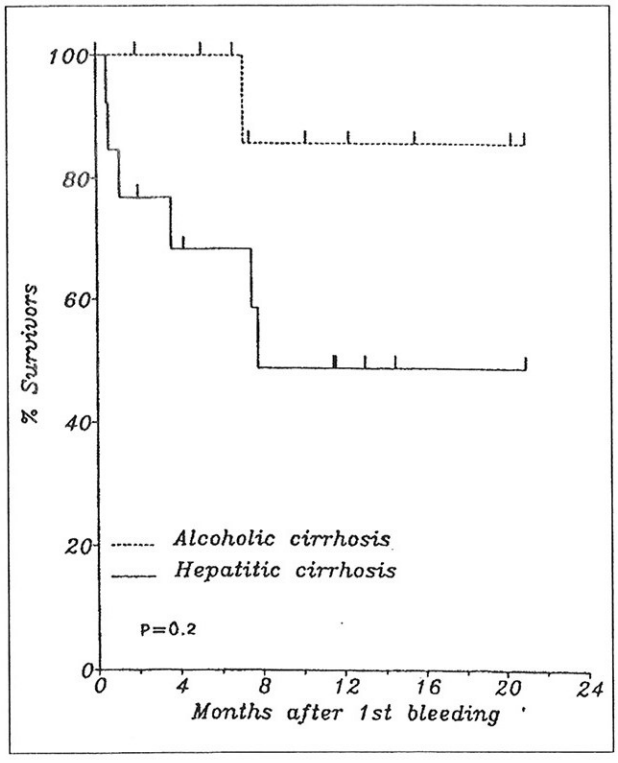

Fig 2 – Survival of patients with Child's C hepatitis-B cirrhosis and Child's C alcoholic cirrhosis treated with injection sclerotherapy following bleeding varices.

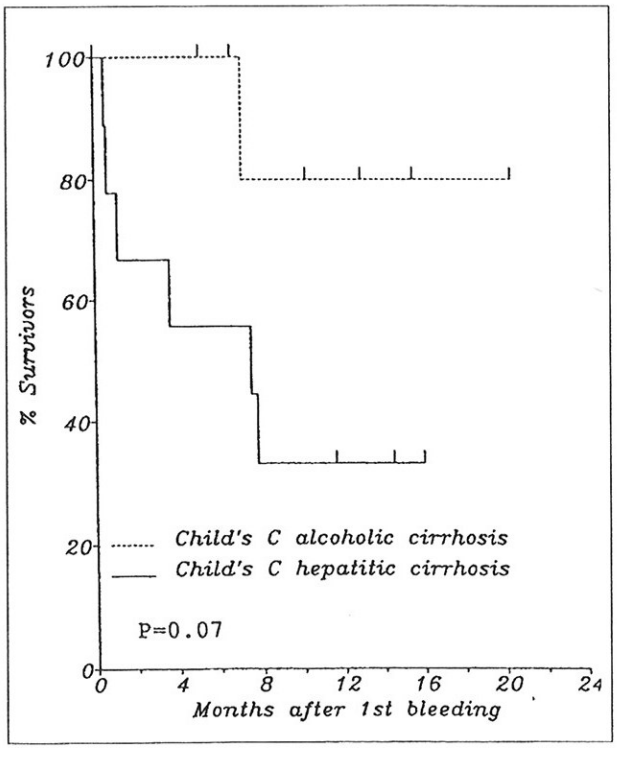

Table IV – Mortality according to Child's classification

Cause of death	Child's Class	
	A/B (n = 14)	C (n = 20)
Liver failure	0	7 (35%)
Variceal bleeding	0	2 (10%)
Respiratory failure	0	1 (5%)
Total*	0	10 (50%)

* Fisher's exact test; p = 0.002

DISCUSSION

All major trials so far[3-8] had alcoholic cirrhosis as the major aetiological group and the consensus opinion is that sclerotherapy reduced mortality and rebleeding frequency after oesophageal variceal bleeding[9]. However, little information is available on the role of sclerotherapy in hepatitis-B cirrhosis following a variceal bleed. Our study shows that hepatitis-B cirrhosis may have a worse prognosis compared to alcoholic cirrhosis in Child's C patients following a variceal haemorrhage with a median survival of 7.5 months after the first variceal bleed whereas no deaths were seen in alcoholic cirrhotics in the first 6 months. The majority of deaths were due to progressive liver failure despite control of variceal haemorrhage. This may be due to the natural history of the hepatitis-B cirrhosis where progressive liver failure continues relentlessly in contrast to alcoholic cirrhosis where the natural history can be altered if the patients stop drinking[16]. Indeed the close supervision of our alcoholic patients resulted in the majority of them abstaining from alcohol. Another possibility is the development of hepatoma in some of these patients during the course of obliterative sclerotherapy despite the negative screening earlier on. Post-mortems were not granted because of local customs and beliefs. The above finding is in contrast to a large follow-up study of 130 patients with hepatitis-B cirrhosis who had not bled where a 5-year survival rate of 55% was observed[17].

Our findings suggest that orthotopic liver transplantation should be considered early after control of the variceal haemorrhage in an attempt to prolong survival in this poor prognostic subgroup with Child's C hepatitis-B cirrhosis eventhough controversy still surrounds the indication for liver transplant due to the high risk of graft infection[18]. However there are evidence to indicate that long term hepatitis-B immunoglobulin in this group of transplanted patients can significantly reduce hepatitis-B reinfection and improve long-term survival with a reported one and three year survival rate of 84% and 67% respectively[19-21].

In conclusion, based on our preliminary finding, variceal haemorrhage in Child's C hepatitis-B cirrhosis is associated with reduced survival with a median survival of 7.5 months compared to Child's C alcoholic cirrhosis, despite control of the bleed. These findings require confirmation in a larger study. It would be interesting to investigate further whether sclerotherapy actually improves survival after variceal bleeding in hepatitis-B cirrhosis as most studies to date had alcoholic cirrhosis as the major aetiological factor. Variceal bleeding represents only one facet of the problem posed by decompensated hepatitis-B cirrhosis and there is little prospect of a really effective treatment for the underlying liver disease. Liver transplantation will undoubtedly be performed with increasing frequency but ultimately, the solution lies in the prevention of hepatitis-B related portal hypertension with hepatitis-B vaccine which was recently introduced in Malaysia for newborns of mothers with positive serology for hepatitis-B.

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