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Clinical trial

Prophylactic endoscopic sclerotherapy of oesophageal varices in liver cirrhosis. A multicentre prospective controlled randomised trial in Vienna

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SUMMARY **The effect of prophylactic treatment of oesophageal varices by endoscopic injection sclerotherapy before the first episode of variceal haemorrhage was studied in patients with cirrhosis in a prospective, randomised and controlled multicentre trial. From February 1984 to March 1987 patients with liver cirrhosis and large varices (stage III–IV according to Paquet) were treated and followed up. The sample comprised 87 patients: 45 in the prophylactic treatment and 42 in the control group. After excluding drop outs, 41 patients were treated in each group. Twenty nine per cent of patients in the sclerotherapy group and 34% in the control group had a variceal haemorrhage during the period of observation. There was no significant difference in the distributions of the bleeding free intervals between the sclerotherapy and the control groups. During the follow up period 24% of patients in the sclerotherapy group and 46% in the control group died. The distribution of survival times indicates a tendency towards longer survival of patients with prophylactic sclerotherapy, particularly in those with alcoholic cirrhosis.**

Severe haemorrhages from oesophageal varices belong to the most serious complications in patients with liver cirrhosis and portal hypertension. About 30 to 70% of patients with liver cirrhosis develop oesophageal varices[1] and some 20–40% of these will eventually bleed.[2] The mortality of the first haemorrhage has been reported to be between 30 and 80%.[3,4] Although many studies from all over the world show that sclerotherapy during the acute bleeding phase will efficiently stop variceal bleeding[5–9] and repeated sclerotherapy after terminating the initial bleeding episode can increase the longterm survival of such patients,[10] the first massive variceal haemorrhage is nevertheless fatal for many patients. It therefore is tempting to speculate whether injection sclerotherapy before the first variceal bleeding (prophylactic sclerotherapy) is preventive and could avoid all the detrimental sequels of variceal haemorrhage. Indeed, first promising results of prophylactic sclerotherapy have been published by Paquet[11,12] already in 1982, but a reduction of the incidence or a delay of the onset of the first variceal bleeding or an improvement of the life expectancy in patients with liver cirrhosis treated by prophylactic sclerotherapy have not yet been established sufficiently.[2] More recently, two controlled studies on prophylactic sclerotherapy of oesophageal varices described no clinical benefit to patients with large oesophageal varices[13] nor to male patients with alcoholic cirrhosis and oesophageal varices,[14] and a third study concludes, that only a subgroup of patients with oesophageal varices and moderately decompensated alcoholic cirrhosis may

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benefit from prophylactic sclerotherapy.[15] We have carried out a similar prospective multicentre controlled randomised trial in Vienna for the evaluation of prophylactic endoscopic injection sclerotherapy of oesophageal varices in patients with cirrhosis. The study protocol was approved by the ethical committee of the Medical Faculty of the University of Vienna in December 1983.

Methods

PATIENTS

Patient recruitment (starting at 1 February 1984) was planned to last for two years. According to an early publication on the subject by Paquet *et al*[11] in the control group two-thirds of patients with stage III and IV varices bled within two years, but only less than 10% in the prophylactic sclerotherapy group. With an estimated number of 35 patients per recruitment year there was a good chance of affirming the benefit of sclerotherapy.

After the beginning of the study less optimistic numbers were reported,[2 16] so that the recruitment phase was extended until the end of 1986. The intended total number of 45 patients per group sufficed to reach significance at the two-sided 0·05 level for assumed bleeding rates 0·4 and 0·15 respectively, with a power of 0·8. Designing an individual trial with rather moderate power for smaller treatment differences seemed justified, as a final judgment of the eventual benefit of prophylactic sclerotherapy would be possible only by combining the results of all running studies on these questions.[17]

Altogether 87 patients have been recruited with the 'intention to treat'; 45 in the group with prophylactic sclerotherapy, 42 in the control group.

The criteria for inclusion in the trial were as follows: (1) liver cirrhosis; (2) presence of large varices in the distal part of the oesophagus; (3) no previous upper gastrointestinal bleeding; (4) no gastroduodenal ulcer at the time of randomisation; (5) no extrahepatic disease that would alter life expectancy; (6) no current treatment with β-blockers, steroids, or D-penicillamine; (7) age of 18 to 75 years; (8) informed consent.

Most patients were recruited from a pre-existing pool of patients with chronic liver disease who had been followed up regularly in the outpatient clinic of the respective medical department. The remaining patients came from new referrals for evaluation of chronic liver diseases. The investigation of such patients included an oesophagogastroscopy for screening of the presence of oesophageal varices and grading them by size according the method of Paquet.[11] All patients were specifically questioned for episodes or signs of upper gastrointestinal bleeding. Only patients with oesophageal varices of stages III and IV according to Paquet[11] who clearly stated that they had never bled and in whom at endoscopy no evidence of oesophageal or gastric bleeding was present were invited to participate in the study. Only seven patients refused to participate and two more patients were not accepted as it was not clear from their case histories whether they had bled before or not. Patients who were eligible and who consented to participate in the trial were randomly assigned to a group receiving sclerotherapy and to a control group. The characteristics of the patients (age, sex, prothrombin time, size of varices,[11] aetiology of liver cirrhosis and Child-Pugh[18] classification) in each study group are summarised in Table 1. There are no serious deviations between the two groups which is partly due to the stratified randomisation for the risk factors, variceal staging and prothrombin time. All patients gave informed consent. Three of the patients, who gave their informed consent shortly before randomisation refused to accept sclerotherapy after randomisation. One of the patients in the sclerotherapy group could not be treated because of the long absence of an endoscopist and died 30 days after randomisation. One patient of the control group after the informed consent and randomisation insisted on sclerotherapy. Altogether there were 41 patients in each group who have been treated according to the rules of the protocol until 31 March 1987. The study conformed with the 1975 Declaration of Helsinki Ethical Guidelines.

Table 1 *Characteristics of patients at entry, according to study group*

	Sclerotherapy n=45 [n=41]	*Control n=42 [n=41]*
Age (yr)	58·8±(10·6) [59·3±(10·5)]	55·3±(12·3) [55·9±(11·7)]
Female	11 [11]	14 [14]
Male	34 [30]	28 [27]
Prothrombin time (%)	60·1 (20·1) [60·6 (20·0)]	62·8 (20·4) [63·2 (22·6)]
Stage of varices		
Paquet III	39 [36]	35 [34]
Paquet IV	6 [5]	7 [7]
Alcoholic cirrhosis	27 [26]	19 [19]
Posthepatitic cirrhosis	8 [6]	13 [13]
Primary biliary cirrhosis	6 [5]	3 [2]
Cryptogenetic cirrhosis	4 [4]	7 [7]
Child-Pugh Group		
A	14 [12]	14 [14]
B	18 [17]	14 [14]
C	13 [12]	14 [13]

*Values in square brackets refer to patients remaining after exclusion of patients who dropped out. Plus-minus values are means (SD).

Table 2 *Number of patients treated by the different endoscopists**

Endoscopist	*RP*	*WR*	*EK*
Sclerotherapy (n)	31 (29)	8 (6)	6 (6)
Control (n)	29 (28)	6 (6)	7 (7)

*Numbers in brackets refer to protocol adhering cases; these are the patients who remain after exclusion of patients who dropped out.

RANDOMISATION

Randomisation was done in groups of four patients stratified with respect to endoscopist, variceal stage (III and IV), and prothrombin time (<30% and >30%). Selection bias was avoided by telephoning the Department of Medical Statistics after recruitment and informed consent of every patient.

METHOD OF SCLEROTHERAPY

Sclerotherapy was carried out with flexible glass-fibre endoscopes GIF K_2 and GIF-IT10 of Olympus. As premedication 5 mg diazepam (Valium^R) was given iv. The injection technique of sclerotherapy was intravascular, as described by Soehendra,[9] but starting with injections of varices situated most proximally in the oesophagus and continuing in craniocaudal direction. As the gastroscope is inserted deeper towards the gastro-oesophageal junction it can exert some compression on the varix injected before. As sclerosing agent a 1% solution of polidocanol (Aethoxysklerol^R) 20 to 40 ml per session was used. After sclerotherapy patients stayed in the hospital for two to three days. Sclerotherapy was done at 0, 4, 8, 12, 16, 24 weeks and then in half year intervals if varices reappeared at follow up. The patients in the control group had oesophagoscopy at the beginning of the study and thereafter every six months. No treatment of portal hypertension or oesophageal varices was made. Clinical follow up was done every three months.

TREATMENT OF VARICEAL BLEEDING DURING THE TRIAL

In case of variceal bleeding after recruitment, treatment in either group consisted of hospitalisation, endoscopical sclerotherapy, blood transfusion, and any additional measures as were clinically needed.

STATISTICAL ANALYSIS

Survival probabilities were estimated by the product limit method of Kaplan and Meier. The comparison of survival curves was performed by the Mantel-Cox-test[10] because differences were expected to exist at rather larger time intervals. Separate analyses were done for the patients with 'intention to treat' and for the patients treated according to the protocol.

Results

DESCRIPTION OF TREATMENT GROUPS

The number of patients treated by the different endoscopists is given in Table 2. The majority of cases has been recruited at the University Clinic of Gastroenterology and Hepatology by a single endoscopist (RP). At the Clinic of Internal Medicine of the Wilhelminen Hospital two endoscopists shared the remaining number of patients. The balance between the two treatment groups is the result of the stratified randomisation with respect to the three endoscopists.

After initial treatment time of a maximum of 24 weeks – that is, a maximum of six sclerotherapy sessions – the varices had completely disappeared in 22 patients. In 15 patients much smaller varices only stage I to II and in four patients varices of stage III were still present at endoscopy. Of the latter four patients in whom the sclerotherapy obviously failed, all eventually died with bleeding: one patient after the first, two patients after the second, and one patient after four sessions.

BLEEDING FREE INTERVAL

The distributions of bleeding free intervals after entering the study did not differ between sclerotherapy and control group. Figure 1 shows the cumulative proportion of patients without bleeding depending on the interval after entering the study; here only patients who were treated according to the protocol have been considered. The Mantel-Cox test for these patients showed a p value of 0·72. Including also the cases with the 'intention to treat' into their

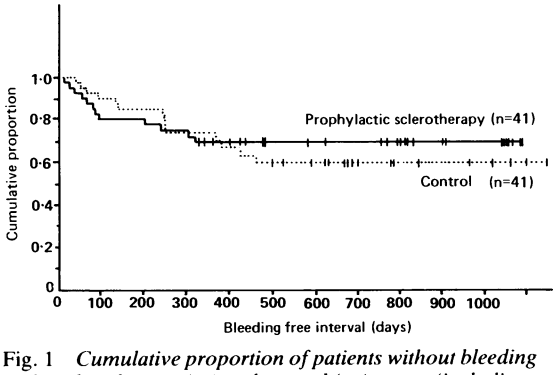

Fig. 1 *Cumulative proportion of patients without bleeding in the sclerotherapy (—) and control (...) group (including only patients treated according to the protocol). Censoring times are marked by vertical bars.*

Table 3 *Further events in patients who started variceal bleeding during the trial and causes of death*

	Sclerotherapy group (n=41)		*Control group (n=41)*	
	n	%	*n*	%
Haemorrhage	12	29·2	14	34·1
	Further events			
	9	Sclerotherapy	11	
	1	Conservative therapy	2	
	2	PC-shunt	0	
	0	Gastrectomy	1	
	5	Death	9	
Death	10	24·3	19	46·3
	Causes of death			
	5	Variceal bleeding	9	
	1	Liver failure	5	
	1	Hepatoma	3	
	1	Pulmonary infarction	0	
	0	Bronchus – CA	1	
	1	St P Liver transplantation	0	
	1	Peritonitis	1	

randomised group, a p value of 0·81 resulted so that both types of analyses led to the same conclusion of no treatment differences. This tendency was homogeneous over the three endoscopists: the p values for the group of protocol adhering cases per endoscopist were 0·96, 0·51, and 0·53. The further events of the patients with haemorrhage are shown in Table 3. In the control group 14 patients bled from oesophageal varices and in 11 of them sclerotherapy could be performed. Despite sclerotherapy, seven of these patients ultimately died from bleeding. Two more bleeding patients of the control group did not reach a hospital in time and died despite conservative treatment by their physicians. One patient underwent gastrectomy and survived.

In the sclerotherapy group 12 patients had a variceal bleeding. One was successfully managed by conservative treatment only (blood transfusion and vasopressin iv), two by portocaval shunt surgery. Nine patients were treated by endoscopic sclerotherapy, but only four patients survived. The other five patients died from bleeding: four bled from varices of stage III and one from stage II varices.

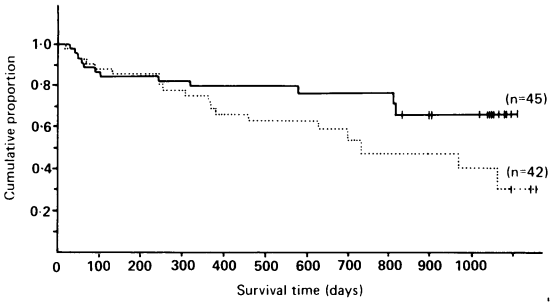

Fig. 2 *Survival curve for the patients in the sclerotherapy (—) and control (...) group (including only patients with the intention to treat). Censoring times at the end of the survival curves are marked by vertical bars (applies also to Figs 3 and 4).*

SURVIVAL

The distribution of survival times indicated a tendency towards longer survival in the group of prophylactic sclerotherapy. Figure 2 shows the survival curves depending on the interval after entering the study for the two treatment groups. All patients with 'intention to treat' have been included (Mantel-Cox-test p=0·059). Analysing only those cases treated according to the protocol, leads to a p value of 0·024. This tendency seems to be particularly accentuated for the patients of the University Clinics (p=0·035); in the second study centre (with considerably smaller number of patients per endoscopist) the resulting p values per endoscopist were 0·45 and 0·68 respectively. For the patient groups with Child classification A, B, and C, the tendency for the difference in survival seemed to be decreasing with increasing severity of the liver disease (p values Child A: 0·014, B: 0·25, C: 0·34). The causes of death are described in Table 3. Table 4 shows the correlation of the causes of death to the Child-Pugh classification of protocol adhering cases.

Looking into the subgroup of patients with alcoholic cirrhosis Figure 3 shows, that the difference in survival exists mainly in this group (intention to treat p=0·024, protocol adhering cases p=0·029). In contrast with patients with non-alcoholic cirrhosis (Fig. 4) no such trend could be found (p=0·66 and

Table 4 Causes of death in correlation to Child classification in protocol adhering cases

	Bleeding	*Hepatic coma*	*Hepatoma*	*Other events*	*Total number of deaths*		
Child A	0	0	0	0	0		
Child B	2	1	1	1	5	10	Sclerotherapy group
Child C	3	0	0	2	5		
Child A	1	0	0	2	3		
Child B	3	1	0	0	4	19	Control group
Child C	5	4	3	0	12		

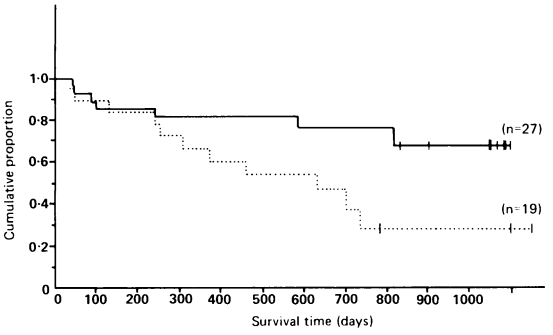

Fig. 3 *Survival curve for the patients with alcoholic cirrhosis in the sclerotherapy (—) and control (...) group (including only patients with the intention to treat).*

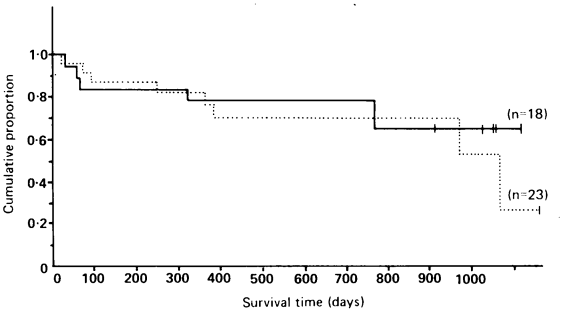

Fig. 4 *Survival curve for the patients with non-alcoholic cirrhosis in the sclerotherapy (—) and control (...) group (including only patients with the intention to treat).*

p=0·26 respectively). The reason for this is the shorter survival of patients with alcoholic cirrhosis and no sclerotherapy. This group clearly deviates from the others (Fig. 3).

Discussion

Only few studies on prophylactic sclerotherapy have been reported[11–15 20–22] and so far no definite answer is available with respect to both the beneficial and adverse effects of endoscopic sclerotherapy before the first episode of variceal haemorrhage. The present trial was designed to study whether prophylactic sclerotherapy of oesophageal varices in patients with cirrhosis of the liver could reduce the incidence of first episodes of variceal haemorrhage and if so, whether this would improve the life expectancy of such patients. As patients at the highest risk of a first variceal bleeding would probably benefit the most from a method aiming at the prevention of such a bleeding, and large oesophageal varices carry a great risk of bleeding,[23 24] only patients with large varices (stage III and IV according to Paquet) were entered into the trial. Surprisingly, in our trial sclerotherapy did not have a significant effect on the incidence of first episodes of variceal bleedings. During the study period of three years 34% of patients in the control group with cirrhosis of the liver and large oesophageal varices experienced a spontaneous variceal haemorrhage and in the sclerotherapy group the incidence of variceal bleeding was still 29%. This finding is in contrast with three earlier studies from Germany[11 20 21] which describe a reduction of bleeding incidence by prophylactic sclerotherapy. These discrepancies could be related to differences in the selection of patients and their randomisation, as in two of these studies the incidence of bleeding was 66%[11] and 57%[21] in the control group, which is almost twice the incidence of variceal bleeding in the control group of the present trial. Interestingly, two recent trials done in the United States[13 14] report a significant increase in the incidence of upper gastrointestinal bleeding in their prophylactic sclerotherapy groups, and thus are also at variance not only with the earlier German studies[11 20 21] but also with the result of the present trial which finds no significant change in the incidence of variceal bleeding after endoscopic sclerotherapy. Although it is tempting to attribute these discrepancies to differences in the skills of the endoscopists rather than to the techniques used, the reason for these discrepancies remains enigmatic. Of course, in the planning stage of this trial we were concerned about the possibility, that the injection sclerotherapy *per se* could induce variceal bleedings. Therefore every patient was kept in hospital for a period of two to three days after each sclerotherapy session. Fortunately, we did not observe a major variceal bleeding during this short period after injection sclerotherapy. Haemorrhages occurring at a later time were not considered as induced by sclerotherapy but were treated statistically (and medically) as a complication of the portal hypertension. From the 12 patients in the sclerotherapy group who bled, seven had a haemorrhage in the first three months of therapy. These haemorrhages possibly started from ulcers next to residual varices. Therefore it might have been better to shorten the interval between sclerotherapy sessions as Sarin has suggested.[25] On the other hand patient compliance might have been endangered by choosing shorter intervals between sclerotherapy sessions. Although the total volume of sclerosant per session used was rather large (20 to 40 ml polidocanol) we did not observe the formation of strictures or ulcers. Unfortunately, one case of mediastinitis subsequently complicated with pulmonary infarction occurred in the sclerotherapy group. The patient died in the intensive care unit 26

days after the second injection sclerotherapy session. Possibly this complication could have been avoided by using a smaller volume of sclerosant.

Although the incidence of first episodes of variceal haemorrhage was not reduced in the sclerotherapy group the distribution of survival times indicates a tendency towards longer survival of patients having undergone prophylactic sclerotherapy particularly in the subgroup of patients with alcoholic cirrhosis. This finding is in contrast with a recent report by Gregory *et al*[14] of an excess mortality in their prophylactic sclerotherapy group of male patients with alcoholic cirrhosis and oesophageal varices, as a result of upper gastrointestinal bleeding and infections. As we did not see infections in our study group and the incidence of variceal bleedings in our sclerotherapy group was not increased, the contradictory results could be caused by differences in patient populations studied and in the techniques of sclerotherapy used.

It is conspicuous that in our trial prophylactic sclerotherapy showed the best result in patients with alcoholic cirrhosis, who experienced an improvement in survival. This totally unexpected finding is in keeping with the most recent published trial of the Study Group of Prophylaxis of Variceal Bleeding in Munich,[15] which also describes a significant improvement in survival of a subgroup of patients with alcoholic cirrhosis who were willing to undergo sclerotherapy. Like Sauerbruch *et al*[15] we think, that the most likely explanation for this finding is that the treatment served as a psychological support for the patients to stop drinking alcohol, while alcoholics in the control group probably continued their alcohol abuse. This explanation is only a guess, however, as we do not have data with respect to drinking habits for the patients in the trial. The finding of an improved survival associated with sclerotherapy in the subgroup of alcoholic cirrhosis could help to interpret differences in the incidence of deaths in Child B and Child C patients: in the sclerotherapy group patients classified as Child B and C showed equal mortality rates, while in the control group only four deaths occurred in Child B but 12 in Child C patients. It is hard to tell whether this difference is of significance, because the numbers are small. This could possibly be explained by the fact that the control group contained more patients with alcoholic cirrhosis in subgroup Child C than in subgroup Child B (eight patients *versus* four patients) and the beneficial effect of sclerotherapy with regard to survival is linked to the subgroup of alcoholic cirrhosis. On the other hand a recent experimental study in Göttingen mini pigs did show a few changes in liver function and an increase in liver blood flow induced by sclerotherapy of experimentally created oesophageal varices.[26] Thus one could at least speculate about a possible similar positive effect of variceal sclerotherapy in patients with cirrhosis of the liver.

In conclusion the results of our trial show, that prophylactic sclerotherapy of large varices (stages III and IV) does not significantly lower the risk of the first variceal bleeding in patients with cirrhosis of the liver. With respect to survival, alcoholics may profit from repeated sclerotherapy. This observation may be related to changes in drinking habits, however, rather than to a positive effect of sclerotherapy itself and needs further clarification. Whether prophylactic injection sclerotherapy of oesophageal varices, started at an earlier stage of portal hypertension, as suggested by Koch *et al*,[20] aiming at the occlusion of small sized varices (stage I, II) would be advantageous, remains open for further investigation.

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