Combined (short term plus long term) sclerotherapy v short term only sclerotherapy: a randomised prospective trial

M Moretó, M Zaballa, E Ojembarrena, S Ibáñez, M-J Suárez, F Setién, E Delgado

Abstract
Short term sclerotherapy (by injection(s) around the bleeding point) is used for immediate control of massive haemorrhage from oesophagogastric varices. The usefulness of long term sclerotherapy once short term sclerotherapy has been successfully carried out was assessed. Two treatment groups were studied: 50 patients were treated by 'combined' (short term followed by long term) sclerotherapy; 56 patients were treated by short term sclerotherapy only. Patients included in the second group were treated by short term sclerotherapy only if a variceal rebleeding was present. The overall cumulative proportion of patients rebleeding was not significantly different in either group. Combined sclerotherapy patients, however, experienced less episodes of variceal haemorrhage and the source of haemorrhage was different (p<0.002). Combined sclerotherapy was more efficient in preventing bleeding from oesophageal bleeding points but not those arising from a junctional source (p<0.05). A greater incidence of oesophageal rebleeding was found in those patients whose first source of bleeding was oesophageal (p<0.05). No significant difference was detected in survival expectancy between either group. In conclusion, after short term sclerotherapy is carried out successfully, those patients with bleeding from variceal bleeding points located on oesophageal mucosa should benefit most from a long term sclerotherapy programme.

Patients and methods

PATIENTS
All patients diagnosed by endoscopy of having bleeding variceal oesophagogastric varices during a four year period were eligible for the trial provided they had not previously been treated by sclerotherapy or other definitive measures. Those patients whose variceal haemorrhage arose from gastric fundus were excluded, but not those bleeding from the 2–3 cm below cardia.

All the patients were initially treated by short term sclerotherapy. If they subsequently remained free of bleeding for a week, an upper endoscopy was carried out. After confirmation of the absence of a haemorrhagical phenomena, and having given their informed consent, the patient was randomised to a group. Randomisation was carried out by opaque sealed envelopes. Patients presenting some variceal haemorrhagical recurrence during the week before randomisation had an emergency endoscopy, with additional short term sclerotherapy if haemorrhagical varices were identified. In such cases randomisation was postponed for another week.

Diagnosis was based on histological or laparoscopic information, or both. Patients with known hepatic carcinoma were excluded. Likewise, two of the included patients were immediately excluded when it was shown they had such a lesion during the follow up.

A total of 106 patients entered the trial: 50 were treated by combined sclerotherapy, starting long term sclerotherapy concurrently with the moment of randomisation. Fifty six were exclusively treated by short term sclerotherapy – that is, they received only local sclerosing injections if a variceal haemorrhagical recurrence was present – aiming to obtain an immediate haemostatic effect.

Recurrences had been registered in 11 patients (10.4%) before randomisation. Six of these were allocated to the combined sclerotherapy group, and five to the short term sclerotherapy group.

ENDOSCOPIC TECHNIQUE
The technique used has been detailed elsewhere. In brief, short term sclerotherapy was performed by injection into the varix immediately distal to the source of bleeding. Five per
cent ethanolamine olate plus bovine thrombin was used as a thrombosclerosing mixture. A vigorous and continuous aspiration was used through the biopsy channel to obtain an adequate fixation of the endoscope as well as a better tolerance for the patient, as we have repeatedly experienced before. After seven days, an upper endoscopy was carried out to determine the effectiveness of the procedure and the possible existence of ulcers after sclerotherapy. Long term sclerotherapy, on the other hand, was performed by injection at the root of the varices, in the cardiac area. In each session, 2–3 varices were injected.

MONITORING
Randomisation day was the zero point of the trial. Patients were visited and treated blindly by one of three gastroenterologists devoted to endoscopy.

Long term sclerotherapy sessions were scheduled every two weeks, until varices disappeared or were of minimum calibre; this, in turn, was followed by an upper endoscopy every six months. If varices reappeared or enlarged, a new sclerotherapy was carried out.

Short term sclerotherapy patients were followed up with clinical visits on a similar schedule: every two months over a six month period followed by one every six months.

If a variceal haemorrhagical recurrence was present, short term sclerotherapy was performed in all patients on an emergency basis.

Patients were reminded by phone when missing an appointment, and were removed from the trial if two absences were recorded. In such cases, the study period was included as censored time.

DEFINITIONS
Site of the bleeding source was made according to the following classification: (a) upper gastric (gastric mucosa 2–3 cm below cardia); (b) cardiac (gastric mucosa placed upon muscular cardia ending at mucosal junction); (c) low oesophageal (lower third); (d) upper oesophageal. These four areas are usually regrouped into two: junctional (the first two) and oesophageal.

Grading of varices – having previously unified the criteria on the basis of endoscopic pictures, varices were subjectively classified into small, moderate, and large. They were subsequently graded as follows: grade I, no more than a moderate varix and none large; grade II, more than one moderate varix or only one large varix, or both; grade III, more than one large varix.

Rebleeding episodes were defined as variceal haemorrhagical recurrence, on emergency diagnostic endoscopy, in the event of: (a) massive variceal bleeding; or (b) presence of oozing, usually at subcardial area; or (c) absence of apparent source of bleeding.

Hypovolaemia was considered to be present when a systolic arterial pressure <100 mm Hg or a heart frequency >100 beats/minute, or both were recorded.

Active alcoholism was defined as a daily ethanol consumption above 100 grams for the past three months before admission.

Liver function has been classified according to Pugh's modification of Child's grading.

DATA MANAGEMENT AND ANALYSIS
In our experience, an expectancy of rebleeding of about 55% within a 30 week period was estimated in patients managed exclusively on a short term sclerotherapy basis. If its usefulness was exclusively limited to haemostatic effect and no preventive action on further rebleeding was to be expected, we could propose a 50% reduction in rebleeding by means of longterm sclerotherapy. According to Freedman's tables, with a power of 80% and a type I error of less than 0·05, the sample size should include about 90–95 patients, taking into account excluded patients (as we were not aware of any report showing a deleterious effect of repeated sclerosing injections on haemorrhagical recurrence, a one tailed analysis was selected). Thus, on this basis, the sample was adequate and we stopped from entering new patients to the study.

The sample size was lessened because subsets were made. To partially correct this drawback, according to the recommendations of Detsky and Sackett, we calculated the confidence intervals of cumulated expectancy with the method described by Simon. On the other hand, the sample size was too small to show a beneficial effect on mortality, using a similar method: expectancy of mortality was of 30% within a 30 week period. To prove the effectiveness of longterm sclerotherapy in reducing this figure to 20%, it would be necessary to include 470 patients (even assuming that longterm sclerotherapy was not expected to increase mortality and one tail analysis was permitted). If the aim was to reduce mortality by half, the sample size would still be too large: 201 patients. Consequently, we used haemostasis as our target, albeit establishing two separate end points in our analysis: the first rebleeding episode and death.

Quantitative variables were analysed by Student's t test, whereas qualitative variables were assessed by the χ² test. Recurrence and survival expectancy have been plotted using the Kaplan and Meier method, with the log rank test for comparison between plots.

Means are reported with standard deviation, and a probability of less than 0·05 has been considered as significant.

Results
Both groups of patients were homogeneous according to clinical, biological, and endoscopic criteria, registered at the initial diagnostic endoscopy examination (Tables I and II).

The follow up period was similar in both groups: mean (SD) 99·8 (77·7) weeks in combined sclerotherapy group vs 113 (86) weeks in short term sclerotherapy patients (p>0·05) (overall range: 1–252 weeks). Table III shows the drop outs from the protocol.

Focusing exclusively on current alcoholic patients, six of 25 combined sclerotherapy
patients continued to drink in an excessive manner. This proportion did not differ significantly when compared with short term sclerotherapy patients (five of 30).

**HAEMORRHAGIC RECURRENCES**

Twenty six combined sclerotherapy group patients suffered from, at least, one episode of rebleeding: in 15, the first recurrence came from the junctional area; in six, it came from the oesophageal mucosa; in two other cases, it was thought to have come from a sclerotherapy related ulcer, and it was impossible to identify the source of bleeding in the remaining three patients. Short term sclerotherapy patients suffering from one or more recurrences amounted to a total of 35 (in 14, the first recurrence came from the junctional mucosa; in another 14, from the oesophageal mucosa; in the remaining seven, the source of bleeding was unknown.

Figure 1 shows that the cumulative expectancy of rebleeding in each one of the groups did not differ significantly.

By comparing the distribution of total amount of episodes of recurrence in each of the groups, grouped by site of bleeding (Fig 2), there was a significant difference with a greater difference on bleeding episodes from oesophageal sites of haemorrhage (p<0.002).

Figure 3 shows individual Kaplan-Meier plots with respect to the source of rebleeding. Short term sclerotherapy patients showed a notably higher expectancy of rebleeding from the oesophageal area than combined sclerotherapy patients (p<0.05; 95% confidence intervals: 0.30 to 0.57 v 0.03 to 0.22). In contrast, a non-significant higher expectancy of bleeding from the junctional area was registered in combined sclerotherapy patients (p>0.05; 95% confidence intervals: 0.31 to 0.69 v 0.25 to 0.55) (Fig 4).

No apparent interdependence was seen between liver function parameters (either considered individually or as Pugh grades), partial thromboplastin time or platelet count, and expectancy of rebleeding.

To predict the patients that would be more at risk of rebleeding from an oesophageal source, using associative criteria, a significant trend was registered for a rebleed from the same site as the first bleeding point (p<0.0005) (Table IV). By contrast, variceal caliber despite suggesting some direct associative trend with oesophageal source of bleeding, did not reach statistical significance.

**ANALYSIS OF SURVIVAL**

No significant difference was detected in survival expectancy between both groups when deaths related to rebleeding were considered as well as when all liver related causes of death were included. Some suggestion of an amelioration of the life expectancy in combined sclerotherapy patients, however, could be inferred from the liver related death figures (Table III).

**COST EFFECTIVENESS**

The number of admissions (mean (SD)) was similar in both groups (combined sclerotherapy/ short term sclerotherapy: 2-5 (2)/2-9 (2-5) admissions/patient). When we restricted our analysis to oesophageal bleeders, longer term sclerotherapy patients spent less days in hospital, although this difference did not reach statistical significance: 31 (25-8) v 37 (33-3) days, p>0.05.

**COMPLICATIONS**

Combined sclerotherapy patients: three cases of rebleeding secondary to ulcers after sclerotherapy were registered; one case of mild oesophageal stenosis without dysphagia; one case of pneumonia with a good response to antibiotic treatment, and seven cases of sclerotherapy-related self limited fever.

Short term sclerotherapy patients: two cases of bleeding ulcer after sclerotherapy, two cases of pneumonia, and eight cases of self limited fever were seen.

**Discussion**

This trial does not contradict the usually accepted view of the usefulness of sclerotherapy in preventing varical haemorrhage, as all the
patients had received sclerotherapy, at least, on one occasion. As it was not possible to rule out initially some protective role against rebleeding by short term sclerotherapy, the prospect of a 50% reduction in rebleeding could seem very optimistic. As there are no substantial data measuring this possibility, we started our trial with the hypothesis that short term sclerotherapy is ineffective against rebleeding. Thus, we selected the 50% rate according to the usual value of the effectiveness of longterm sclerotherapy v controls. We found only a statistically insignificant 10% decrease at 30 weeks in the expectancy of rebleeding, which favoured combined sclerotherapy (Fig 1). We cannot rule out a real, albeit small, difference favouring combined sclerotherapy over only short term sclerotherapy (to corroborate it on statistical grounds would require around 280 patients). It seems more relevant, however, to emphasise that while longterm sclerotherapy shows no apparent additional effectiveness in preventing further junctional variceal bleeding once the patient has received short term sclerotherapy, it would significantly do so if we limited our attention to oesophageal rebleeding. Therefore, it is possible that no or a detrimental action of longterm sclerotherapy on some subsets of patients could bias the overall results. Consequently it is debatable as to the benefit of including a patient in a longterm sclerotherapy programme if it is aimed at preventing junctional recurrences. As subsets of patients were made, the sample size has become considerably lessened and a type II error cannot be ruled out. Future studies will be welcomed on this subject. While there is no overlapping of rebleeding expectancy ranges in respect to oesophageal recurrence, there is a strong suggestion against such a difference when junctional rebleeding expectancy is analysed.

A double mechanism could be at the base of the apparent selective beneficial effect of longterm sclerotherapy on oesophageal rebleeding. According to Vianna et al.,11 veins should show a dense palisade arrangement at the junctional area. We may speculate that, by sclerosing the cardiac area, an interruption of ascendent flow is obtained. Some bleeders initially from an oesophageal source, however, rebled from junctional sources. Dilawari et al. have found12 that many patients with extrahepatic portal hypertension, after receiving sclerotherapy, develop large splenoadrenorenal shunts. Patients who did not, were the most prone to have variceal haemorrhagic recurrence. Unfortunately, angiographic studies were usually not available in the patients in this trial.

It would be of considerable practical interest to find out those patients who are more prone to future oesophageal rebleeding. From our results, it can be inferred that the oesophageal source of the initial bleeding would help to foresee further oesophageal sites of haemorrhage. Other indicators, such as variceal size, red spots or angiographic aspects should be evaluated in further trials. A more precise prediction of risk of oesophageal rebleeding should be relevant to the cost effectiveness not only by permitting a reduction in sclerotherapy sessions but also to reduce hospital admissions as,
although it is possibly not a definitive conclusion, a trend towards less hospital days in combined sclerotherapy patients was seen when we restricted our analysis to oesophageal bleeders. In both groups, recurrences arising from unidentified sources have been registered. Some could be related to congestive gastropathy. Congestive gastropathy has been shown to be induced by longterm sclerotherapy and was thought to be the cause of several cases of readmission during the trial. In such cases, bleeding is in a subdued manner and endoscopic diagnosis is usually more difficult or even merely speculative.

In conclusion, longterm sclerotherapy can be considered as a useful tool for prophylaxis against oesophageal recurrences, but possibly it does not add any prophylactic effect against junctional recurrences to that obtained exclusively by short term sclerotherapy. Patients with a bleeding source located on oesophageal mucosa should benefit from a longterm sclerotherapy programme. On the other hand, those patients whose first bleeding arose from gastric mucosa around the cardia and once haemorrhage had been stopped (unless there was an oesophageal recurrence) could be considered for alternative measures (possibly pharmacological or surgical), to reduce the risk of variceal haemorrhagic recurrence.

We particularly thank Pilar Rodríguez for her secretarial assistance and the nurses of the endoscopy unit for their expert and dedicated care of the patients included in this trial.

8. Detsky AS, Sackett DL. When was a negative clinical trial big enough? How many patients you needed depends on what you found. *Arch Intern Med* 1985; 145: 709-12.

### Table IV

<table>
<thead>
<tr>
<th>Same category of varix</th>
<th>Combined sclerotherapy</th>
<th>Short term sclerotherapy</th>
<th>Combined sclerotherapy</th>
<th>Short term sclerotherapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oesophageal bleeding</td>
<td>6/22</td>
<td>11/22</td>
<td>1/28</td>
<td>8/34</td>
</tr>
<tr>
<td>Junctional bleeding</td>
<td>16/28</td>
<td>15/34</td>
<td>8/22</td>
<td>5/22</td>
</tr>
<tr>
<td>Total</td>
<td>22/56</td>
<td>26/56</td>
<td>9/50</td>
<td>13/56</td>
</tr>
</tbody>
</table>

Overall proportion: 48/106*\( \times 2 = 96/106 \times 2 = 192/212 \times 0.005.\)