Leading articles

Variceal sclerotherapy: further progress

Variceal bleeding can be spectacular with a mortality varying from 15 to 50%. The use of vasopressin, glypressin or the Sengstaken-Blakemore tube will stop the bleeding temporarily, but with little effect on eventual mortality. Portacaval shunting stops the bleeding, but at the expense of an increased chance of encephalopathy and no overall improvement in mortality.¹ Even the distal splenorenal shunt devised by Warren to protect hepatic blood flow and lessen encephalopathy appears to have little advantage over the old portacaval shunt.²

The rediscovery of endoscopic sclerotherapy has revolutionised the management of bleeding varices. First described in 1939, it then lapsed into relative obscurity until the 1970s, when the new aggressive breed of physician endoscopists elbowed their surgical colleagues out of the way and injected sclerosant into any vein that dared to bleed. The honeymoon period was soon replaced by a phase where the complications, some of them fatal, and the failure to show an improvement in mortality,³ led to a reassessment of technique. The surgeons again came back into the reckoning with the advent of the anastomotic gun, and transection of the lower oesophagus gave results as good as those of sclerotherapy.⁴

This led to a critical re-examination of sclerotherapy techniques. Investigation of sclerosants,⁵ treatment intervals,⁶ the number of injections, the use of tamponade or overtubes, and sites of injection have yielded a more scientific approach to the obliteration of varices, with better results and fewer complications. Flexible endoscopes and diazemuls analgesia are as effective as the more complex methods involving rigid endoscopes, overtubes or compressing devices. It is also reassuring to note that in an animal model Jensen *et al*⁵ found sclerotherapy able to provide reliable haemostasis for almost all acutely bleeding canine varices, while the heater probe would control bleeding in only 50%; other methods including the argon laser, bipolar electrocoagulation and monopolar electrocoagulation, were even less effective.

The major difference in sclerotherapy techniques is whether the sclerosant is injected into the varix to obliterate the lumen (the Anglo American method), or into the lamina propria and submucosa alongside the varix (the European approach), so as to produce inflammation initially followed by a wall of fibrosis to cover the vessel. Which is better? In a small study published in 1983 intravariceal injection, as determined by radiological screening of a urografin-sodium tetradecyl sulphate mixture, thrombosed eight of 10 varices with no complications, while paravasal injection thrombosed only three of 10 varices and was significantly ($p < 0.05$) less successful.⁷ One iatrogenic ulcer which bled was produced by paravasal injection and another patient complained of dysphagia for some weeks. These results have now been confirmed in a large prospective controlled trial.⁸ The intravariceal technique was not only significantly more effective

in controlling active variceal bleeding than the paravariceal route, but also eradicated the varices in approximately half the time with less retrosternal pain and fewer variceal recurrences.

Is this result conclusive? Should all paravasal sclerotherapists now give up and join the intravariceal school? Sarin and his colleagues used a transparent Teflon injector and determined that they were in the varix by the aspiration of blood into the injector. Two to three injections spread 2 cm apart were given into each variceal column until blanching was seen. But blanching suggests that the sclerosant may have been injected partly paravariceally, and the chances of this happening were increased by multiple injections into each varix (a single injection just above the gastro-oesophageal junction will usually suffice to deal with the perforating veins joining the varices to the perioesophageal veins, where bleeding normally occurs⁹). Furthermore, Sarin describes nine instances of fever, 10 of transient dysphagia, four of oesophageal ulcer and four of stricture, all of which are associated with extravasation of sclerosant.

Using a mixture of urografin and STD, intended intravariceal injection in one in five large varices and one in three small varices were actually paravariceal.⁷ In another similar study, 44% of attempted intravariceal injections resulted in paravariceal extravasation of contrast.¹⁰ It has also been estimated that 10 to 15% of paravariceal injections end up intravariceally.¹¹

It therefore seems likely that some of Sarin's intravariceal injections may have been paravariceal. There is, however, other work to support his conclusions. Soehendra¹² found the paravariceal technique required a longer period of treatment with a higher risk of recurrent bleeding. This would explain why the large Copenhagen trial of paravariceal sclerotherapy took 40 days to show an improvement in survival in the treated, compared with the untreated control group.¹³

Absolute alcohol was used by the Indian workers¹⁴ who had earlier found it to be effective, safe, and economical. Jensen *et al*, found injections of 2 ml of 95% ethanol in a canine model to cause too much oesophageal damage and ulceration for clinical use, however, and 47% ethanol, as used in Sarin's current paper, to be ineffective.⁵

What conclusions should be drawn? The intravariceal route is better than the paravariceal. One injection per varix only is necessary, just above the gastro-oesophageal junction where the oesophageal perforating veins lie.⁹ The injections should be given weekly.⁶ Sodium tetradecyl sulphate is probably the best available sclerosant,⁵ and if the volume used is limited to 2 ml or less, oesophageal strictures are rarely seen. Without the use of a Teflon injector or a monitoring device some injections will be paravariceal, but provided a small volume of sclerosant is used, full thickness oesophageal wall ulceration should not occur.

And what of alternative therapies after the acute bleeding episode has passed? In 1980 Lebrech *et al* reported that propranolol would reduce the wedged hepatic venous pressure by decreasing cardiac output and, secondarily, splanchnic and hepatic blood flow.¹⁵ A controlled study of propranolol in patients with oesophageal varices and cirrhosis followed, which showed an improvement in survival rate and a decreased rebleeding rate over two years in comparison with a placebo group.¹⁶ As the same workers had earlier found that there was no relationship between the portal venous pressure and

the risk of variceal haemorrhage,¹⁷ it was surprising that propranolol should work. A British trial, however, again conducted over two years, found no decrease in bleeding in the propranolol treated group.¹⁸

A recent study from Montreal has also failed to find a significant difference in bleeding incidence or in survival at one and two years after a prospective randomised single blind trial of propranolol.¹⁹ It therefore seems that the best alternative treatment for bleeding varices, if sclerotherapy fails, is transection. Combining transection with devascularisation of the lower oesophagus, Johnston⁴ treated 80 patients with bleeding varices with a hospital mortality of only 14% and a three year survival of 69%, comparable with the best figures for sclerotherapy. Encephalopathy was not a problem, although late recurrent bleeding occurred in 14 patients, and for this reason transection should be followed up by endoscopy exactly as if successful sclerotherapy had occurred.

There have been a number of randomised clinical trials of chronic sclerotherapy, but of these the South African trial³ and the Los Angeles trial²⁰ failed to show an improvement in the survival of the treated group. The Copenhagen Oesophageal Varices Sclerotherapy group compared conventional therapy with paravariceal injection of polidocanol.¹³ Cirrhotic patients with bleeding varices were randomised as soon as possible after emergency endoscopy. There was no significant difference in the number of patients who rebled from varices during the first 40 days, but after that survival improved progressively in the sclerotherapy group so that long term survival at 40 months was statistically better. The King's College Hospital trial followed up 116 patients for a mean of 37 months.²¹ Thirty four patients were not included in the trial, however, because of rapid clinical deterioration and death within 48 hours of admission. Intravenous injections of ethanoleamine oleate were started one to five days after the bleeding had been stopped and were repeated at three weekly intervals until the varices were obliterated. Both the survival and the rebleeding rate were significantly improved by sclerotherapy, almost all the rebleeding episodes occurring before variceal disappearance.

Can we therefore conclude that sclerotherapy really does work, or are the differing results from the trials merely a reflection of the time of patient admission to the study after the initial variceal bleed, bearing out the statement that 'the longer a patient survives, the better is his prognosis'.²² Graham and Smith²³ stressed the importance of the time elapsed from the onset of bleeding to the entry of subjects into a study as a major contributor to prognosis. In their own publication, there was a high mortality of 36% in the first two days, so the survival curves were much worse the earlier in the course of variceal haemorrhage the calculations were started.

Bullimore²⁴ has now looked at the problem afresh in a study of 144 unselected patients, with a mortality rate of only 3% at two days and 35% at three months and with far fewer alcoholics than Graham and Smith. Not surprisingly, the survival curves for the British patients differ little from each other whatever the time of entry to the trial. Bullimore points out that groups of patients admitted to a study two to 12 weeks after the initial bleed, with survival calculated from the time of entry to the study, would have similar survival curves, and the difference between survival curves can be accentuated by a relatively short follow up period and by using retrospective analysis.

It has also been suggested that studies of survival figures by national referral centres are biased by the inclusion of good risk patients referred from the periphery. Such patients are believed to have a better prognosis because they have survived the first variceal bleed long enough to be stabilised and transferred. Bullimore, however, in a review of the same 144 patients, found that survival to discharge was 70% in the local and 74% in the peripheral group. Survival depended not on peripheral referral bias, but much more on Child's grading.²⁵

We must therefore look elsewhere to determine why the South African and Los Angeles trials failed to show survival advantage for sclerotherapy. In Cape Town further episodes of bleeding in the control group were treated for ethical reasons with acute sclerotherapy, leading to complete or partial disappearance of varices in 37% of the control group, and presumably an improved survival.³ In Korula's trial, 21% of the patients were lost to follow up, and in only 28 of the original treatment group of 63 was variceal obliteration achieved. Despite this, the trial did confirm a reduction in bleeding in the sclerotherapy group, and if the patients undergoing shunt surgery were excluded from analysis, there was a significant difference in favour of the sclerotherapy group.²⁰

It therefore seems reasonable to conclude that sclerotherapy really does improve the mortality of bleeding varices. If the injections are aimed intravariceally at weekly, rather than three weekly intervals, then the varices will disappear faster and the patient is less liable to exsanguinate in the period before variceal obliteration occurs. The problem of the underlying liver disease remains, however. Perhaps the Chancellor should have increased the tax on alcohol after all.

PAUL M SMITH

*Llandough Hospital,
Cardiff*

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