

# Intravariceal versus paravariceal sclerotherapy: a prospective, controlled, randomised trial

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**SUMMARY** Fifty four consecutive patients with oesophageal variceal bleeding were randomised to undergo intravariceal (28 patients) or paravariceal (26 patients) sclerotherapy, every three weeks. Intravariceal technique was found significantly ( $p < 0.01$ ) more effective in controlling active variceal bleeding than the paravariceal technique (91% v 18.7% respectively). The mean ( $\pm$ SD) time taken for variceal eradication by intravariceal sclerotherapy ( $15.4 \pm 5.3$  weeks) was significantly ( $p < 0.001$ ) less than paravariceal ( $26.8 \pm 6.6$  weeks) technique. The number of sclerotherapy sessions needed with intravariceal technique were also significantly less. Rebleeding was seen in 38.5% patients after para and 14.3% after intravariceal injections (NS). Except for retrosternal pain, which occurred more often ( $p < 0.01$ ) with paravariceal technique, there was no difference in the incidence of other complications or mortality between the two groups. Variceal recurrence was seen in seven patients (25%) in the intra and one (3.9%) patient in the paravariceal group ( $p < 0.01$ ) after a mean follow up of  $29.4 \pm 9.1$  weeks. Intravariceal sclerotherapy was superior to paravariceal in the control of active variceal bleeding and for total variceal obliteration, but was associated with a higher variceal recurrence.

There are probably as many variations in the technique of sclerotherapy as there are endoscopists practising it.<sup>1,3</sup> Many of the technical variations may, however, be more apparent than real. The use of modified endoscopes,<sup>4,5</sup> William's semirigid overtube,<sup>6</sup> balloon tamponade after sclerotherapy, etc, has declined over the years, as variceal haemorrhage could be managed equally satisfactorily with flexible endoscopes without accessories.<sup>2,3,7</sup> One of the important and basic questions which remains unanswered, however, is the ideal site for the injection of the sclerosant – inside (intravariceal) or along the side (paravariceal) of the vein. A large number of studies are available in which either intra or paravariceal technique<sup>2,12</sup> or a combination of the two<sup>13</sup> have been used. The present study was initiated to compare the efficacy of intra and paravariceal techniques of sclerotherapy for the treatment of oesophageal varices in a prospective, randomised, controlled manner.

## Methods

### PATIENTS

Between February and September 1985, 54 patients with endoscopically diagnosed oesophageal varices were included in the trial. The patients were randomised using a table of random numbers to either intravariceal or paravariceal sclerotherapy regimen immediately after admission. The demographic profile, the aetiology of portal hypertension, and the clinical presentation of the patients undergoing the two sclerotherapy treatment schedules is shown in Table 1. No patient was excluded from the trial because of massive bleeding or hepatic encephalopathy. The nature of the treatment was explained to the patients and their relatives and the necessity for strict adherence to the protocol was stressed. Severity of the underlying liver disease was graded at the time of presentation according to Child's classification.<sup>14</sup> Size of the oesophageal varices was graded from 1 to 4.<sup>15</sup>

Patients were classified at the time of sclerotherapy into (a) active bleeders – patients with fresh active spurting or oozing of blood from the varices at the

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Received for publication 10 October 1986.

Table 1 Clinical profile of patients in the two sclerotherapy groups

Parameter	Intravariceal (n=28)	Paravariceal (n=26)
Age (yrs)	32.0+11.4	28.4+7.6
Sex (M:F)	15:13	16:10
Bleeding		
Active	7	6
Old	21	20
Aetiology		
Cirrhosis	14	13
Non-cirrhotic portal fibrosis	6	9
Extrahepatic portal obstruction	5	4
Hepatic venous outflow obstruction	3	-
Child's grade		
A	13	16
B	6	9
C	9	7
Grade of varices		
2	3	1
3	7	5
4	18	20

time of endoscopy or (b) old bleeders – patients who were not bleeding at the time of endoscopic sclerotherapy, but had bled in the past. Rebleeding was defined as any bleeding before the next course of sclerotherapy, diagnosed at emergency endoscopy to be occurring from varices; a thorough search for any associated cause for bleeding being negative.

All patients who rebled during the trial period, were injected on an emergency basis after the original intra or paravariceal schedule. As a policy, use of Sengstaken – Blackmore tube was withheld until emergency endoscopic sclerotherapy was considered a failure.<sup>7</sup> After control of the acute episode, resclerotherapy was done after three weeks according to the initial protocol.

#### TECHNIQUE

For both intra and paravariceal injections, an indigenously designed, transparent, Teflon injector with a 21 gauge needle (23 gauge for paediatric patients), and a flexible fiberoptic endoscope (Olympus GIF Q,P 2 or XP) was used. Fifty per cent ethanol was used as a sclerosant. Intravariceal sclerotherapy was done according to the technique described earlier.<sup>2</sup> Briefly, the variceal injections were given starting from the lower end of the variceal columns near the cardia. After puncturing the varix, the blood could immediately be seen to flow up into the Teflon injector. The sclerosant was injected until an area of 0.5 to 1.0 cm of 'blanching' was seen. Two to three injections spaced approximately 2 cm apart were given in each column. Areas showing oesophageal ulcers caused by previous sclerotherapy

were avoided and injections were given 2–3 cm away.

For patients with continued active variceal bleeding, emergency intravariceal sclerotherapy was done.<sup>7</sup> Emergency sclerotherapy was done immediately after admission or detection of the variceal bleeding. In patients with shock, resuscitative measures were carried out to stabilise the blood pressure above 60 mm Hg before sclerotherapy. During emergency sclerotherapy, an attempt was made to identify the bleeding spot. If this could be located, the injections were first given below the bleeding spot and then around it. If, however, the bleeding point could not be seen, the lower ends of all the variceal columns were injected. Excessive air insufflation and constant suction and flushing with water were found useful while carrying out sclerotherapy during continued bleeding. The endoscope was withdrawn after achieving haemostasis and decompressing the stomach.

Paravariceal injections were given into the submucosa starting from the gastro-oesophageal junction and proceeding upwards. One to two millilitres of the sclerosant, sufficient to raise a small bleb around the needle, was injected along the sides of the variceal columns at distances ranging from 1.0–2.0 cm. For cases with fresh active bleeding or rebleeding, paravariceal sclerotherapy was done on an emergency basis. Injections were restricted to only lower 3–4 cm of the oesophagus during active bleeding.

In both the treatment schedules, repeat sclerotherapy was done at intervals of three weeks, until variceal obliteration was achieved. Variceal eradication was accepted with the consensus of two independent observers, when no variceal column was visible around the circumference of the lower oesophagus. Presence of an occasional tiny remnant, measuring up to 0.5 cm in size, was considered inconsequential, and consistent with variceal eradication.<sup>10</sup> All patients were followed up with monthly endoscopies after variceal obliteration. The trial ran up to the end of the follow up period or death of a patient.

#### STATISTICAL ANALYSIS

Students *t* test and  $\chi^2$  test with Yates's correction, were used. Significance was accepted at  $p < 0.05$ .

#### Results

The aetiology and the clinical presentation of the two groups of patients undergoing intra or paravariceal sclerotherapy, showed no significant differences (Table 1). The transparent Teflon injector used enabled us to record with certainty whether unintended para or intravariceal injections were given.

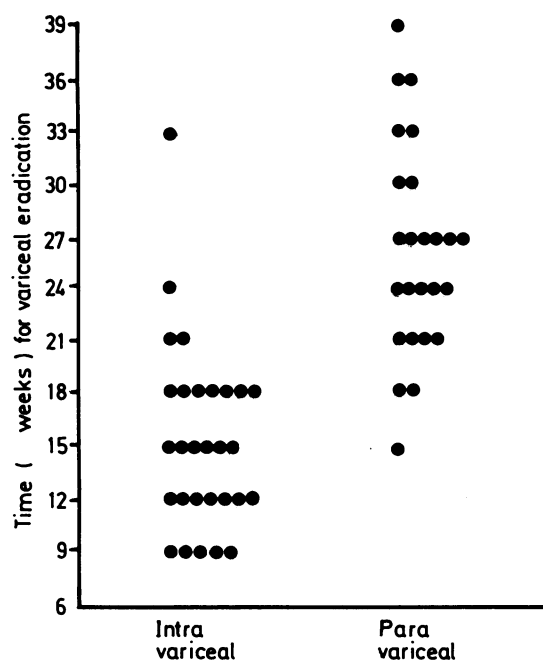


Fig. 1 Time (weeks) required for variceal eradication in individual patient with intra or paravariceal sclerotherapy.

The incidence of undesired injections was 9%. This was more common with paravariceal technique, especially when carried out in active bleeders.

CONTROL OF ACTIVE BLEEDING

Of the 11 patients who underwent emergency intra-variceal sclerotherapy for active bleeding, seven had come with a fresh bleed and four had rebled while on sclerotherapy. Bleeding could be successfully controlled in all but one (90.9%) patient with the help of intravariceal injections. In the paravariceal group, 16 patients, six with fresh and 10 with a rebleed, received emergency sclerotherapy. It was successful in controlling the bleeding in only three (18.7%) subjects. The difference in the success rate between the two techniques was highly significant ( $p < 0.01$ ).

VARICEAL ERADICATION

The 'kill time' or the time required for variceal eradication by patients being treated with the intra-variceal (median 15 weeks, range 9–33) regimen, was significantly ( $p < 0.01$ ) shorter compared with the paravariceal (median 27 weeks, range 15–39) regimen (Fig. 1, Table 2). Moreover, the number of injections needed per session for adequate sclerotherapy was significantly ( $p < 0.001$ ) more with the paravariceal technique. The mean ( $\pm$ SD) amount of

Table 2 Comparison of the efficacy of the two techniques of sclerotherapy\*

Parameter	Intravariceal (n=28)	Paravariceal (n=26)	P
Time (weeks) taken for variceal eradication	15.4 $\pm$ 5.3	26.8 $\pm$ 6.6	<0.001
Sclerotherapy sessions per patient (n)	5.5 $\pm$ 1.4	8.3 $\pm$ 3.5	<0.01
Injections per session (n)	3.9 $\pm$ 2.1	9.1 $\pm$ 3.4	<0.001
Sclerosant per patient (mc)	75.3 $\pm$ 36.7	91.6 $\pm$ 47.8	NS
Complications			
Retrosternal pain	8 (28.6) <sup>†</sup>	21 (80.0)	<0.01
Fever	9 (32.1)	11 (42.3)	NS
Rebleeding	4 (14.3)	10 (38.5)	NS
Transient dysphagia	10 (35.7)	13 (50)	NS
Oesophageal ulcer	4 (14.3)	2 (7.7)	NS
Stricture	4 (14.3)	3 (11.5)	NS
Oliguria	2 (7.1)	–	
Death	2 (7.1)	6 (23.1)	NS
Recurrence of varices	7 (25)	1 (3.9)	<0.01

\* The value of various parameters is shown as mean + SD; <sup>†</sup> The figures in parentheses indicate percentages; NS=not significant.

sclerosant required per patient was not, however, different with the two techniques (Table 2).

COMPLICATIONS

In general, both the techniques were found safe and easy to do. The most common complaint of the patients undergoing paravariceal therapy was retrosternal pain and its incidence (81%) was significantly higher ( $p < 0.01$ ) than in patients undergoing intravariceal sclerotherapy (29%). Pain usually developed at the time of the paravariceal injections and lasted for four to 24 hours after sclerotherapy.

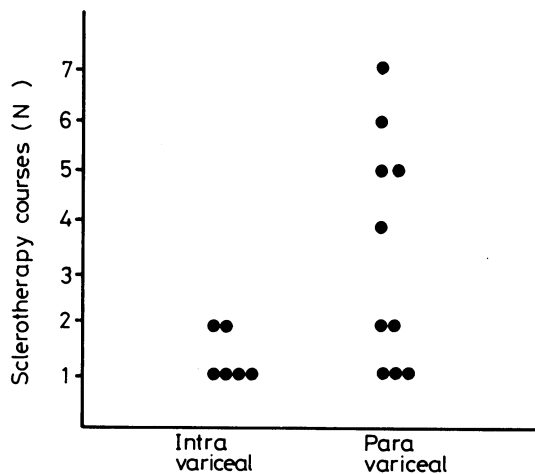


Fig. 2 Frequency of rebleeding after intra or paravariceal sclerotherapy courses.

Rebleeding was seen more frequently after paravariceal (38.5%) injections than intravariceal (14.3%), the difference was, however, not significant (Table 2). With both treatment modalities, rebleeding was more common during the initial three courses of sclerotherapy. With paravariceal therapy, rebleeding was often seen even after four courses of injections. (Fig. 2). There was no significant difference in the frequency of other complications in the two treatment groups (Table 2). The approximate blood loss, assessed visually at the time of sclerotherapy was much less, and sometimes negligible with paravariceal compared with intravariceal technique.

During a mean ( $\pm$ SD) follow up of  $29.4 \pm 9.1$  weeks (range 22–61) the variceal recurrence was seen in one (3.2%) patient in paravariceal and seven (25%) patients in intravariceal sclerotherapy group. The difference was significant ( $p < 0.01$ ). These veins were injected at the time of follow up endoscopies which were done regularly at monthly intervals. None of the patients with variceal recurrence had a bleed.

#### MORTALITY

There were eight (14.8%) deaths, two (7.1%) in the intravariceal and six (23.1%) in the paravariceal group. None of the deaths in the intravariceal group was caused by bleeding. Both the patients who died had advanced cirrhosis (Child's C) of the liver and had succumbed to end-stage hepatic failure. Five of the six patients who died in the paravariceal group, had cirrhosis of the liver (three had Child's C and one each had Child's B and A) and one patient had non-cirrhotic portal fibrosis. Three patients (two cirrhotic and one non-cirrhotic) died of rebleeding and the other three died of hepatic coma.

#### Discussion

Intravariceal and paravariceal techniques of sclerotherapy are theoretically quite different. Intravariceal therapy aims at obliteration of the varices by direct injection of the sclerosant into the varix and inducing venous thrombosis. Paravariceal injections on the other hand, provoke a proliferative inflammation in the submucosa with subsequent fibrosis and reinforcement of the wall between the varices. The lumen of the varices is expected not to get obliterated and portal decompression function of the collaterals is thus, believed to be preserved with paravariceal injections.<sup>9,12</sup>

The results of the present study, the first comparative report of its kind to our knowledge in English literature, indicate that paravariceal sclerotherapy was of limited success (18.7%) in controlling active variceal bleeding compared with intravariceal

technique (91%); the difference was highly significant. Similar disappointing results with paravariceal technique in acute bleeding have been reported by many other workers.<sup>9,10,13</sup> Stray *et al* have, however, reported successful control of 10 of the 11 (91%) episodes of active variceal bleeding with paravariceal injections.<sup>16</sup> As a Sengstaken tube was used immediately after emergency paravariceal sclerotherapy in most of their patients, however, it is possible that part of their success could be due to the balloon tamponade. Paquet has recently claimed 90% success in control of active variceal bleeding with paravariceal technique.<sup>17</sup>

Variceal eradication could be achieved significantly early with intra compared with paravariceal technique. The number of sclerotherapy sessions required and the number of injections per session were also significantly more with the paravariceal technique. A long variceal eradication period required with paravariceal technique, has been reported by many workers.<sup>8,10,12</sup> Rose *et al* using a sclerosant contrast mixture showed that intravariceal sclerosant injections were more effective than paravariceal injections in producing vascular thrombosis.<sup>18</sup> Anderson *et al* despite doing aggressive sclerotherapy every third day, recorded 48% rebleeding within the first 40 days with paravariceal sclerotherapy.<sup>9</sup> Paquet has, however, reported only 6% rebleeding rate with paravariceal technique. The lower rebleeding rate in his series could possibly be due to performing prophylactic sclerotherapy. Rebleeding was seen in 38.5% patients after para and 14.3% after intravariceal sclerotherapy in our patients. The difference was not significant; possibly because of the small number of patients. It appears however, quite clear that one of the main disadvantages of the longer 'kill time' with paravariceal technique is the higher incidence of rebleeding and possibly consequent higher mortality.

Retrosternal pain was seen significantly more often after para than intravariceal injections. The incidence of other complications was not different between the two groups. As paravariceal technique invokes a fibroproliferative response in the submucosa of the oesophagus, it is thought that it may be associated with a higher incidence of oesophageal ulceration and stricture formation. In fact, dysphagia and oesophageal stricture formation after paravariceal therapy have been reported in up to 59% of patients.<sup>19</sup> We found on the other hand that the incidence of both oesophageal ulceration and stricture formation after paravariceal sclerotherapy was low and comparable with intravariceal technique. We have shown recently that oesophageal ulcers may be a necessary accompaniment rather than a complication of sclerotherapy<sup>20,21</sup> and therefore, may have little

direct influence on oesophageal stricture formation.<sup>22</sup>

There was no significant difference in the mortality rates between the two groups. Three patients died in the paravariceal group, however, because of uncontrolled bleeding. Because the intravariceal technique was found successful in controlling active bleeding in the present as well as the earlier studies,<sup>27</sup> we feel that it is preferable to the paravariceal technique in patients with continued active variceal bleeding.

Certain technical points in reference to paravariceal therapy are worth mentioning. Despite the wide bore needle of the indigenous injector, a considerable amount of pressure and force was required to give paravariceal injections. The sclerosant could therefore be injected, relatively slowly. Alcohol, the sclerosant used is a low density, low viscosity, aqueous solution and the problem of slow injection with the paravariceal technique is likely to be met more often than if the oily sclerosants like ethanolamine oleate or polidocanol are used. Another disadvantage of the paravariceal technique is the relatively large number of injections required per session. Most workers recommend giving 20–50 injections, each of 0.5–1.0 ml.<sup>9,10,16</sup> Paravariceal sclerotherapy was generally a relatively bloodless procedure and was found to be advantageous in patients with large varices. Another advantage of the paravariceal injections was the non-blockage of the injector needle.

The two groups of sclerotherapy patients were followed up for a mean period of 29.4±9.1 weeks. Seven (25%) patients in the intra and one (3.9%) in the paravariceal group showed variceal recurrence within this period; the difference was significant. The lower incidence of variceal recurrence with paravariceal injections may be because besides inducing submucosal fibrosis, they possibly obliterate the perforating vessels which play a significant role in variceal bleeding and recurrence.<sup>23</sup>

Our results argue in favour of intravariceal sclerotherapy as the technique of choice for the treatment of oesophageal varices as it is not only more effective than paravariceal sclerotherapy in the control of active variceal bleeding but it also eradicates oesophageal varices relatively faster. It remains to be seen, however, whether in the long term, paravariceal sclerotherapy has the advantage of a lower incidence of variceal recurrence over the intravariceal technique.

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