Respiratory function after injection sclerotherapy of oesophageal varices

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Abstract

Arterial oxygen tension (Pa_{O_2}), carbon dioxide tension (Pa_{CO_2}), and vital capacity were measured preoperatively and one day postoperatively in patients with chronic hepatic cirrhosis having elective oesophageal injection sclerotherapy under general anaesthesia. The results were compared with the same measurements made in patients with chronic cirrhosis anaesthetised and scheduled to have injection sclerotherapy under general anaesthesia but who, because of variceal obliteration, only had an oesophagogastroscopy. In the injected group Pa_{O_2} decreased by 9·3 (3·0) mm Hg (1·2 (0·4) kPa) (mean (SEM)) ($p<0·02$) but in the controls did not change. The difference between the two groups was significant ($p<0·02$). Vital capacity decreased by 0·39 (0·08) litres (BTPS) ($p<0·01$) after injection sclerotherapy but in the controls did not change. Again the difference between the two groups was significant ($p<0·02$). In the injected group there was a significant correlation between the change in Pa_{O_2} and the percentage change in vital capacity ($r=0·787$, $p<0·01$) but no such relation was seen in control subjects. These results suggest that oesophageal injection sclerotherapy is associated with a restrictive defect in respiratory function one day after the injection caused, possibly, by sclerosant embolising to the lung.

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Injection sclerotherapy is widely used for the control of the acute oesophageal variceal bleed and obliteration of the varices. The complications of injection sclerotherapy have been extensively reviewed.[1] They can be divided broadly into two categories, those occurring at the site of injection and those resulting from systemic dissemination of the sclerosant through the paraoesophageal and azygos veins; this has been shown radiologically.[2] Abnormalities of organ function have been described including abnormal chest radiology[3] and, more rarely, respiratory failure.[4] Injection of varicose veins in the legs has also resulted in acute renal failure.[5]

The mechanism whereby sclerosants influence pulmonary function has been investigated in experimental animals in some detail; intravenous administration of 20 ml of either ethanolamine oleate or sodium tetradecyl sulphate in sheep resulted in an increase in extra vascular lung water, and a significant decrease in arterial oxygen tension (Pa_{O_2}).[6] It was suggested that these effects were caused by sclerosant embolising to the lung, but in another study intravenous administration of ethanolamine (0·5 ml/kg) resulted in a rapid fall in circulating platelets and leucocytes, with sequestration of platelets in lung, liver, and kidney.[7] Karacagil *et al* thought that respiratory failure after intravenous injection of sclerosant was caused by intravascular platelet aggregation. It has not yet been established, however, whether some degree of respiratory impairment occurs in all patients receiving injection sclerotherapy. This study was therefore undertaken to find out if routine elective injection sclerotherapy for oesophageal varices is associated with any measurable deterioration in respiratory function postoperatively and if any changes occur after sclerotherapy in circulating platelet and leucocyte concentrations.

Methods

PATIENTS

Patients were studied who had hepatic cirrhosis and portal hypertension and were scheduled to have elective sclerotherapy of their oesophageal varices under general anaesthesia. All had received injection sclerotherapy on at least one previous occasion. Those who, in the event, were injected were designated the treatment group and those who, because of variceal obliteration, had oesophagogastroscopy only were used as controls. Informed consent was obtained and the study was approved by the local ethics committee. Severity of liver disease was determined at the time of each injection using Child's classification.[8]

STUDY DESIGN

Three studies were performed altogether on three separate groups of patients; in one, the respiratory function study, respiratory function tests (blood gases and vital capacity) and white cell and platelet counts were performed preoperatively and one day postoperatively. The second study, the perioperative white cell and platelet study, was carried out on a separate group of patients; white cell and platelet concentrations were measured preoperatively, and up to one hour after the procedure. The third study – sclerosant and the coagulation cascade study – was done in vitro to find out if the sclerosant had any effect

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Demographic and clinical data of patients in whom respiratory function was studied and those having serial white cell and platelet counts done before and after injection sclerotherapy (injected) or oesophagogastroscopy (non-injected)

	Sex distribution	Age (y)	Weight (kg)	Severity of liver disease (Child's classification at time of treatment)
Respiratory function study				
Injected	8M, 4F	45–72 (median 55)	47–76 (median 63)	A:2, B:8, C:2
Non-injected	6M, 3F	40–59 (median 56)	46–76 (median 62)	A:2, B:5, C:2
Perioperative white cell and platelet study				
Injected	5M, 5F	46–69 (median 57)	49–80 (median 64)	A:1, B:7, C:2
Non-injected	4M, 1F	49–63 (median 56)	51–76 (median 60)	A:1, B:3, C:1

on the coagulation cascade of patients' plasma or the plasma of normal volunteers.

RESPIRATORY FUNCTION STUDY

In 21 patients scheduled to have injection sclerotherapy Pa_{O_2} and Pa_{CO_2} were measured the day before and the day after the procedure. Blood gas measurements were made using an ABL2 blood gas apparatus (Radiometer, Copenhagen, Denmark). Blood was obtained from the radial artery (under local anaesthesia) with the patient propped up in bed at about 60°. Vital capacity was measured using a wedge spirometer (Vitalograph, Buckingham, UK) with the patient, on all occasions, sat on the edge of the bed. Platelet and total white cell counts were performed the day before and the day after the procedure. Chest x rays were taken routinely before and within six hours of injection sclerotherapy.

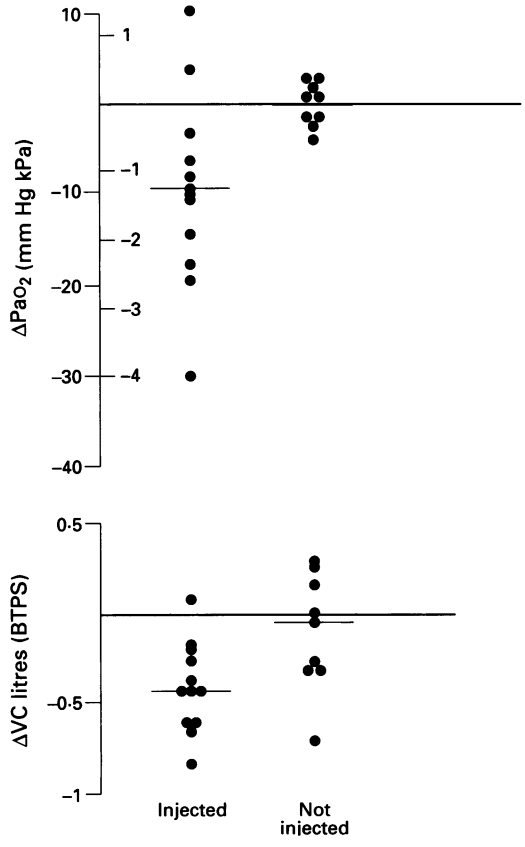

Figure 1: Changes in Pa_{O_2} (ΔPa_{O_2}) and vital capacity (ΔVC) in two groups of patients with hepatic cirrhosis and portal hypertension scheduled for oesophagogastroscopy and oesophageal injection sclerotherapy under general anaesthesia. The 'injected' group received injection sclerotherapy, non-injected in the event had only oesophagogastroscopy. The difference in ΔPa_{O_2} and ΔVC between the two groups is significant ($p<0·02$).

General anaesthesia and surgical procedure

All oesophageal procedures were performed under general anaesthesia. This is now fairly unusual but at the time was the general policy of the department. No preoperative drugs were given. Anaesthesia was induced with thiopentone (175–350 mg), and suxamethonium (75–100 mg) was used to facilitate endotracheal intubation. The lungs were ventilated with nitrous oxide:oxygen (2:1 ratio) and enflurane was added as judged necessary. Incremental doses of suxamethonium were used for muscle relaxation until a decision had been made whether or not to inject the varices. If the decision was made to inject each patient received 15 mg atracurium, and its effect was reversed at the end of the procedure with neostigimine (2·5 mg) and atropine (1·2 mg). Those patients who did not undergo injection sclerotherapy received incremental doses of suxamethonium until the end of the oesophagogastroscopy. No patient was anaesthetised for longer than 30 minutes.

Injection sclerotherapy was carried out with a Williams Overtube. All varices were injected intravariceally with ethanolamine oleate.

Platelets and white cells

Platelet and white cell counts were performed the day before and the day after the procedure.

PERIOPERATIVE WHITE CELL AND PLATELET STUDY

Platelet and white cell counts were performed perioperatively on a separate group of 15 patients scheduled for elective sclerotherapy. Blood was taken after induction of anaesthesia and immediately, 10 minutes, and one hour after completion of the injection. If the varices did not require injection blood was taken at the termination of the oesophagogastroscopy, 10 minutes later, and one hour later.

SCLEROSANT AND COAGULATION CASCADE STUDY

Evidence of direct activation of coagulation pathways was sought by determining prothrombin, thrombin, and partial thromboplastin times by standard methods in the presence and absence of serial dilutions of ethanolamine oleate, on blood taken from three patients and pooled plasma from normal volunteers. Similarly platelet aggregation in platelet rich plasma, measured by a light transmission method, was determined to a standard agonist in the presence and absence of ethanolamine oleate.

STATISTICAL ANALYSIS

Data were analysed using Student's t test for paired and unpaired data as appropriate

and by linear regression analysis. Values are presented as mean (SEM) or as ranges and medians.

Results

RESPIRATORY FUNCTION STUDY

Patients

In the group in which respiratory function was measured 12 patients received injection sclerotherapy; nine had only oesophagogastroscopy. One patient was in both groups – that is, on one occasion the varices were injected, on another she was given an oesophagogastroscopy only. The two occasions were five months apart. The Table shows patients' details and Child's severity grading.

Respiratory function measurements

Arterial P_{O_2} in the injected group was 94·8 (1·91) mm Hg (12·64 (0·26) kPa) preoperatively and one day after the procedure had decreased by 9·3 (3·0) mm Hg (1·2 (0·4) kPa) ($p<0·02$). In the group that was not injected preoperative Pa_{O_2} was 93·8 (2·8) mm Hg (12·5 (0·37) kPa) and postoperatively was 93·8 (3·5) mm Hg ((12·5 (0·46) kPa) (Fig 1). The difference between the two groups was statistically significant ($p<0·02$). There was no change in Pa_{CO_2} in either group.

Vital capacity decreased by 0·39 (0·08) litres (BTPS) ($p<0·01$) in patients who received injection sclerotherapy but did not change in the non-injected group (Fig 2). The difference between the two groups was significant ($p<0·02$). In the group that was injected there was a significant linear correlation between the decrease in Pa_{O_2} and the percentage decrease in vital capacity $r=0·784$, $p<0·01$ (Fig 2).

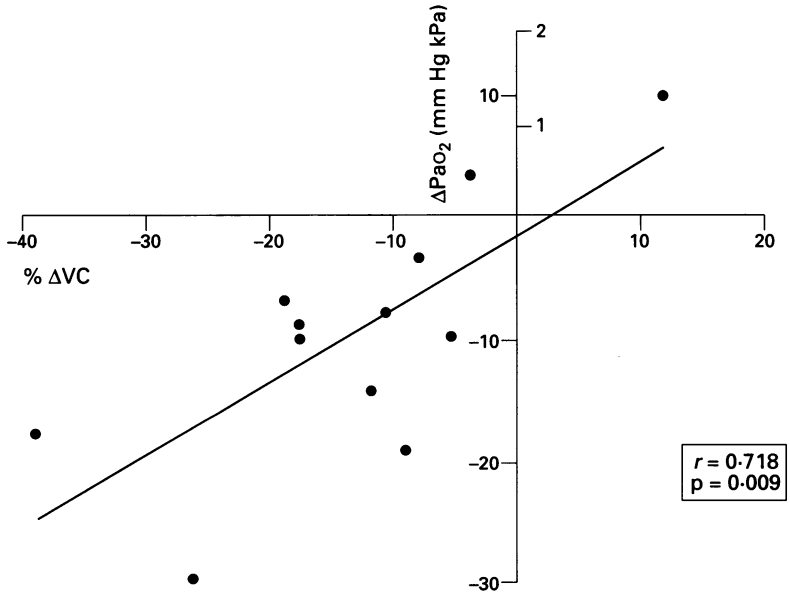

Figure 2: Relation between change in Pa_{O_2} and change in vital capacity in patients with hepatic cirrhosis and portal hypertension who had oesophageal injection sclerotherapy under general anaesthesia.

White cells and platelets

Preoperatively total white cell count was 5·8 (5·5 to 6·3) $\times 10^9$/litre (median (range)) in the injected group and 5·5 (4·6 to 6·2) $\times 10^9$/litre in the controls. The corresponding figures for platelet concentrations were 128 (120 to 138) and 121 (102 to 137) $\times 10^9$ respectively. One day after the procedure there was no change in white cell or platelet count in either group.

In the patients receiving injection sclerotherapy the median volume of ethanolamine oleate injected was 7·5 (range 4–15) ml. In patients who had injection sclerotherapy there was no correlation between the volume of sclerosant injected and the decrease in Pa_{O_2} ($r=0·18$; $p=0·58$). No change was seen in the postoperative chest x ray of any patient compared with the preoperative film and no patient complained of retrosternal pain postoperatively.

PERIOPERATIVE WHITE CELLS AND PLATELET STUDY

Patients

White cell and platelet concentrations were measured perioperatively in 10 patients who had injection sclerotherapy and five who had oesophagogastroscopy only. One patient was common to both groups. Her oesophagogastroscopy (alone) took place five weeks after the injection sclerotherapy. In the patients receiving injection sclerotherapy the median volume of sclerosant injected was 7·8 (range 3–15) ml. The Table shows patients' details and Child's severity grading.

White cells and platelets

The preoperative results were as follows: injected; platelets 152 (139 to 186) $\times 10^9$/litres, total white cells 5·8 (5·5 to 6·2) $\times 10^9$/litre, neutrophils 3·1 (2·9 to 3·2) $\times 10^9$/litre. Non-injected; platelets 119 (97 to 138) $\times 10^9$/litre, total white cells 5·2 (4·8 to 5·7) $\times 10^9$/litre, neutrophils 3·2 (3·0 to 3·4) $\times 10^9$/litre. White cell and platelet concentrations did not change perioperatively.

SCLEROSANT AND COAGULATION CASCADE STUDY

There was no direct evidence of any change in the coagulation cascade shown upon exposure of platelet rich or platelet poor plasma to serial dilutions of sclerosant.

Discussion

The results of this study show a small but measurable restrictive defect in respiratory function after injection sclerotherapy for oesophageal varices. Arterial P_{O_2} decreased in the injected group but not in the controls, and vital capacity decreased in the injected, but again in the non-injected patients did not change. There was a significant correlation between the decrease in Pa_{O_2} and the percentage decrease in vital capacity in the injected

patients ($p<0.01$). The most obvious explanation for this deterioration in respiratory function is the embolisation of sclerosant to the lung, but other possibilities include intravascular platelet aggregation,[7] the inevitable difference in anaesthetic time between the injected and the control group, and differences between the two groups in severity of the cirrhosis.

The only circumstances in which a relation has ever been shown between hypoxaemia and duration of anaesthesia has been in the first few minutes of recovery,[9] resulting from nitrous oxide diffusion, and after major surgery only when the operation lasted for longer than three hours.[10] In surgery lasting up to three hours anaesthetic time has never been shown to make any difference to postoperative Pa_{O_2}.[11 12] In this study Pa_{O_2} was measured the day after the procedure when the effects of all the anaesthetic agents had worn off. No anaesthetic lasted longer than 30 minutes, so the anaesthetic time could not account for the difference in the changes in Pa_{O_2} and vital capacity between the groups. Anaesthesia itself had no effect on respiratory function as there was no change in Pa_{O_2} or vital capacity in the non-injected control group.

Circulating platelet and leucocyte concentrations did not change, so intravascular platelet aggregation as suggested by Karacagil *et al*[7] is unlikely to have accounted for these findings, although this possibility cannot be ruled out completely as white cells and platelets in the peripheral blood could have been replaced as rapidly as they were consumed but there was no evidence of platelet activation with in vitro testing. The dose of sclerosant Karacagil gave to rabbits corresponds to 35 ml in a 70 kg adult; sclerosant doses in both of our studies ranged from 4–15 ml, so in terms of sclerosant volume there is an obvious difference between our study and theirs.

Another explanation for the decrease in Pa_{O_2} could be the severity of the cirrhosis. Portal systemic shunting of blood occurs in decompensated cirrhosis and this results in the delivery of endotoxins, etc, directly from the gut to the systemic circulation. This can affect platelet aggregation mechanisms, coagulation, and ultimately pulmonary function.[13] Cirrhosis is associated also with low platelet counts and prolonged clotting times. It is thus possible that differences in the severity of the cirrhosis (and thus of hepatic shunting) might indirectly affect postoperative respiratory function by an effect on coagulation mechanisms. In both of our studies, however, there was no difference in platelet and white cell counts between the injected and non-injected groups and the severity of the liver disease in the injected and non-injected groups on both occasions was comparable (Table), so differences in severity of the cirrhosis is also unlikely.

There is an incidence of retrosternal discomfort after injection of oesophageal varices,[14] which might be expected to affect respiration, although in our experience the severity of the pain is not normally affected by breathing. No such pain was experienced by any of our patients.

In normal circumstances the lung volume that determines Pa_{O_2} is functional residual capacity. It is a complex measurement that could not be made in present circumstances, but in acute restrictive defects, such as the decrease in lung volume seen after upper abdominal surgery, changes in vital capacity and functional residual capacity tend to parallel each other.[15] The close correlation between the decrease in Pa_{O_2} and the fall in vital capacity suggest that a decrease in lung volume was the probable cause of the drop in Pa_{O_2} described here and resulting perhaps from a decrease in compliance. The most probable explanation would be sclerosant embolising, by the paraoesophageal and azygos veins, to the lung resulting in areas of alveolar exudate and consolidation with an increase in lung stiffness and pulmonary shunt. If that were the case it would be expected that a correlation between the decrease in Pa_{O_2} and the volume of sclerosant injected would be seen. Such a relation was not shown, but as the proportion of sclerosant entering the circulation would vary from patient to patient[2] depending on conditions of local blood flow, previous obliteration of the varices, etc, and the fact that some of the injectate might inevitably go extravariceal, this is perhaps not surprising.

An earlier study that investigated lung function in some detail failed to find any relation between variceal injection and change in Pa_{O_2}.[16] The patients in that study, however, were treated under diazepam and pethidine sedation. Both drugs are respiratory depressants; they have a comparatively long duration of action and both groups in that study showed a decrease in Pa_{O_2} postoperatively. The patients in this study were given only small doses of short acting muscle relaxants and an inhalational anaesthetic agent and were ventilated; also the group that was anasthetised and not injected showed no change in respiratory function. Any small differences in the earlier study could have been obscured by the effects of the prolonged sedation.

In summary patients undergoing elective oesophageal injection sclerotherapy develop a restrictive defect in respiratory function one day after the procedure, which is small but nevertheless detectable, with a decrease in both Pa_{O_2} and vital capacity. The most probable explanation for this finding is the embolisation of the sclerosant to the lung. Whether the same phenomenon occurs after injection of varicose veins in the leg awaits investigation.

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