Randomised trial of octreotide for long term management of cirrhosis after variceal haemorrhage

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Abstract

Objective: To assess the efficacy of long term octreotide as adjuvant treatment to programmed endoscopic sclerotherapy after acute variceal haemorrhage in cirrhotic portal hypertension.
Design: Randomised clinical trial.
Setting: University hospital.
Subjects: 32 patients with cirrhotic portal hypertension.
Interventions: Programmed injection sclerotherapy with subcutaneous octreotide 50 µg twice daily for 6 months, or programmed injection sclerotherapy alone.
Main outcome measures: Episodes of recurrent variceal bleeding and survival.
Results: Significantly fewer patients receiving combined octreotide and sclerotherapy had episodes of recurrent variceal bleeding compared with patients given sclerotherapy alone (1/16 *v* 7/16; P = 0.037, Fisher's exact test), and their survival was significantly improved (P < 0.02, log rank test); this improvement was maintained for 12 months after the end of the study. Combined treatment also resulted in a sustained decrease in portal pressure (median decrease −6.0 mm Hg, interquartile range −10 to −4.75 mm Hg, P = 0.0002) compared with sclerotherapy alone (median increase 1.5 mm Hg, interquartile range 0.25 to 3.25 mm Hg), as well as a significant improvement in liver function as assessed by plasma concentrations of bilirubin, albumin, and alanine aminotransferase and by hepatocyte metabolism of aminopyrine labelled with carbon-14.
Conclusion: Long term octreotide may be a valuable adjuvant to endoscopic sclerotherapy for acute variceal haemorrhage in cirrhotic portal hypertension.

Introduction

Endoscopic sclerotherapy or band ligation is widely used to control acute variceal haemorrhage and reduce recurrent variceal haemorrhage, but rebleeding occurs in up to 50% of patients before variceal obliteration is achieved.[1–5] Furthermore, the effect of both treatments on survival is controversial.[3–5] Despite the central role of endoscopic treatment for variceal haemorrhage, underlying portal hypertension remains unaltered by this treatment, accounting for a continued risk of rebleeding even after variceal obliteration.[1–5] Consequently, there is interest in the use of vasoactive drugs, to assist in acute management,[6] and as adjuvant[7] or even alternative[8] treatment to programmed endoscopic treatment. However, only β blockers have been subjected to randomised clinical trials in this context, with inconclusive results.[7]

An alternative pharmacological approach is afforded by somatostatin[9] and its analogues.[10 11] These agents cause splanchnic arteriolar constriction[12] and inhibit the release of peptides contributing to the hyperdynamic circulatory syndrome of portal hypertension.[13] Although native somatostatin has a short plasma half life of under three minutes,[9] its synthetic analogues have more prolonged effects.[10 11] Octreotide is a synthetic analogue with a plasma half life of over 1 hour in normal people and longer in cirrhotic patients. Subcutaneous octreotide administration results in a sustained reduction of portal pressure and azygos blood flow.[14] These observations, together with possible stimulation of the hepatic reticuloendothelial system,[15] suggest that octreotide may be beneficial in the long term management of cirrhotic portal hypertension. We conducted a randomised controlled trial to examine the effects of long term octreotide treatment in cirrhotic patients after acute variceal haemorrhage.

Patients and methods

Patient evaluation—Entry was confined to patients with cirrhosis confirmed by biopsy after a first variceal bleed. Variceal bleeding was controlled in all patients with two sessions of injection sclerotherapy, and the patients were readmitted to hospital for assessment of their liver disease 3 weeks after their initial presentation. Liver biopsy was performed, and the degree of hepatic dysfunction graded according to the criteria of Child and Turcotte.[16] Portal pressure was measured indirectly by measuring wedged hepatic venous pressure through the femoral vein and subtracting vena cava pressure to determine the hepatic venous pressure gradient. Hepatocyte function was measured by breath testing with aminopyrine labelled with carbon-14,[17] and the activity of the hepatic and splenic reticuloendothelial system was measured by single photon emission computed tomography using sulphur colloid labelled with technetium-99.[18]

Patient recruitment—As octreotide had not previously been used long term in cirrhotic patients after variceal haemorrhage, there were no data to inform a power calculation. Thus pragmatic considerations determined that the sample size was the number of patients who would complete the trial within three years. Thirty two patients satisfying the entry requirements were randomly allocated treatment after complete assessment of their liver disease and 6 weeks after the onset of their first variceal bleed. A randomisation code with equal numbers of the alternative treatments was generated, using random number tables which were unknown to the clinicians allocating treatment to patients. Randomisation was done with sequentially numbered, sealed envelopes using the previously determined code to either the combination of octreotide (Sandoz Pharmaceuticals, Camberley)

and injection sclerotherapy or injection sclerotherapy alone. The study was approved at the outset by the Royal Liverpool University Hospital Ethics Committee, and all patients gave informed consent.

Injection sclerotherapy was carried out using ethanolamine oleate and an intravariceal technique (aliquots of 2 ml, maximum of 20 ml) every 3 weeks until all oesophageal varices were obliterated.

Octreotide—Patients randomly allocated combination treatment received 50 µg octreotide subcutaneously twice daily for 6 months. Patients were taught to self administer between breakfast and lunch, with the second injection 12 hours later before retiring. The use of octreotide vials could not be checked as they had to be kept refrigerated. Placebo injections and blinding were not used as it was anticipated that these would have reduced compliance.

Recurrent bleeding—Patients who had recurrent variceal bleeds were admitted and treated by injection sclerotherapy as above. In some patients endoscopy showed haemorrhage from oesophageal ulcers, which were then treated with somatostatin 250 µg/h.

End of trial—Six months after entry into the trial all surviving patients were readmitted for reassessment as in the initial evaluation (without liver biopsy).

Statistical analysis—Non-parametric methods were used throughout the statistical analysis.[19] Categorical measurements were tabulated for each group and compared using a two tailed Fisher's exact test or χ^2 analysis. Results of continuous measurements were summarised using medians, interquartile ranges, and 95% confidence intervals. Comparisons between the two patient groups were performed using Mann-Whitney U tests, survival was plotted using the Kaplan-Meier method, and the log rank test was used to assess differences in outcome between the two groups.

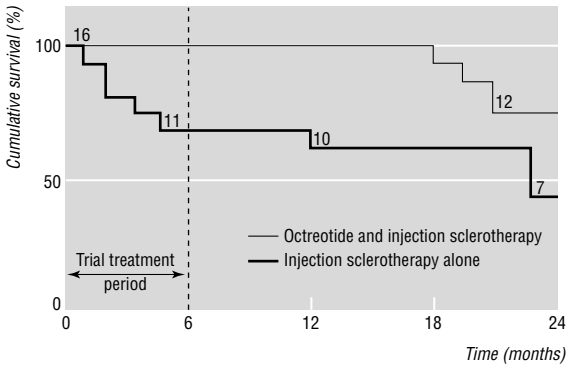
Results

Characteristics of patients

The two groups of patients were well matched in age, sex, severity of liver dysfunction, cause of liver disease, and hepatic venous pressure gradient (table 1).

Rebleeding

During the 6 months of the trial, variceal haemorrhage occurred in one of the 16 patients receiving combined treatment, whereas seven patients receiving only injection sclerotherapy rebled from varices, two of them on two occasions. This difference was significant (P = 0.037, Fisher's exact test). Two patients rebled from oesophageal ulcers, one in each group.



Kaplan-Meier survival plot of patients treated with octreotide and injection sclerotherapy or sclerotherapy alone. Numbers denote surviving patients

Table 1 Demographic details of patients randomly allocated to either octreotide and injection sclerotherapy or sclerotherapy alone. Values are numbers of patients unless stated otherwise

	Octreotide and injection sclerotherapy	Injection sclerotherapy alone
Patients (men:women)	16 (8:8)	16 (10:6)
Median age (interquartile range) (years)	59.0 (51.5-62.0)	55.5 (41.5-65.0)
Child's grade:		
A	2	4
B	10	7
C	4	5
Cause of cirrhosis:		
Alcoholism	12	11
Primary biliary disease	2	2
Unknown	1	3
Chronic active hepatitis	1	0
Median hepatic venous pressure gradient (interquartile range) (mm Hg)	25.4 (20.0-31.5)	22.3 (21.0-27.5)

Table 2 Changes in Child's grade in patients treated with octreotide and injection sclerotherapy or sclerotherapy alone. Values are numbers of patients

	Octreotide and injection sclerotherapy		Injection sclerotherapy alone	
Child's grade	At randomisation	At end of trial	At randomisation	At end of trial
A	2	16	4	8
B	10	0	7	3
C	4	0	5	5*

* At time of readmission during which patient died.

Survival

During the 6 months of the trial 5 patients died, all in the group receiving sclerotherapy alone; 4 died after recurrent variceal bleeding. At the end of the trial patients receiving the combined treatment showed a significant improvement in survival compared with those receiving sclerotherapy alone (P < 0.02, log rank test), and this was maintained for 12 further months, but no longer. This improvement was maintained for about 12 months after the end of treatment (figure).

Other measures

All measures at 6 months include only patients alive at 6 months, other than Child's grade. Child's grade is given at 6 months, except for the patients who died before the trial ended: their grade is given at entry and at the readmission when they died (table 2).

The hepatic venous pressure gradient in patients receiving combined treatment was reduced at 6 months compared with pretreatment values (median change −6.0, interquartile range −10 to −4.75 mm Hg). In contrast, hepatic venous pressure gradient in patients treated by sclerotherapy alone increased slightly at 6 months (median change 1.5, interquartile range −0.25 to 3.25 mm Hg). The difference between treatments was highly significant (P = 0.0002) and in favour of a reduction in the hepatic venous pressure gradient after combined treatment in the range −13 to −6 mm Hg (95% confidence interval of the difference between treatments).

Table 3 Changes in circulating concentrations of albumin, bilirubin, and liver enzymes in patients treated with octreotide and injection sclerotherapy or sclerotherapy alone

	Octreotide and injection sclerotherapy median change (interquartile range)	Injection sclerotherapy median change (interquartile range)*	95% CI for difference between treatments	P value for difference between treatments
Albumin (g/l)	6.0 (7.0 to15.0)	–0.5 (–3.5 to 7.5)	–1.99 to 9.99	0.001
Bilirubin (μmol/l)	–10.0 (–77.0 to –18.0)	1.5 (–55.8 to 19.7)	–52 to –0.01	0.04
γ-Glutamyl transferase (U/l)	–5.0 (–35.2 to 46.8)	0.5 (–4.7 to 55.8)	–5.0 to 58	0.95
Alkaline phosphatase (U/l)	26.0 (–3.0 to 66.7)	–1.0 (–20.3 to 51.7)	1.1 to 51.9	0.05
Alanine aminotransferase (U/l)	–5.5 (–25.0 to –6.0)	3.5 (–28.5 to 33.5)	–27 to 16.0	0.05
Aminopyrine breath test (%)†	1.9 (1.23 to 2.79)	–0.16 (–0.50 to 0.00)	1.44 to 2.74	< 0.0005

*Excludes 5 patients who died before end of trial.
†Cumulative excretion of ^{14}C-carbon dioxide over 2 h.

Child's grade at 6 months in patients receiving combined treatment improved significantly when compared with the grade in patients receiving sclerotherapy alone (P = 0.0002, table 2). Similarly, combined treatment was associated with a significant improvement in liver function assessed by plasma concentrations of bilirubin, albumin, and alanine aminotransferase, as well as by hepatocyte metabolism of ^{14}C-aminopyrine (table 3). In contrast, the reduction in alkaline phosphatase concentrations was less with combined treatment (table 3). There was no significant difference in the median change of γ-glutamyl transferase before and after treatment between the two groups of patients (table 3).

The activity of the hepatic and splenic reticuloendothelial system, as assessed by the uptake of ^{99}Tc-sulphur colloid, was similar in the two groups before treatment. At 6 months there was a significant improvement in activity with combined treatment compared with sclerotherapy alone (table 4).

Treatment complications

The complications of octreotide treatment were minor and consisted of transient diarrhoea at the start of treatment (3 patients) and pain at the site of injection (5 patients). One patient with a history of cholelithiasis developed biliary colic while taking octreotide. Two patients bled from oesophageal ulcers after injection sclerotherapy, one from each group.

Discussion

The results of this trial indicate that the combination of octreotide and injection sclerotherapy is superior to sclerotherapy alone in reducing recurrent variceal bleeding in cirrhotic portal hypertension. Furthermore, the addition of long term octreotide improved the survival of patients beyond the time of obliteration of their varices, suggesting that indefinite improvement might be maintained with indefinite treatment. The improvement in survival is probably related to the reduction in recurrent haemorrhage, since 4 of the 5 deaths with sclerotherapy alone followed recurrent variceal bleeding.

The reduced incidence of recurrent variceal haemorrhage with combined treatment may in turn have been associated with a sustained decrease in the hepatic venous pressure gradient. Thus at 6 months the gradient was reduced by about 25% with combined treatment but not with sclerotherapy alone. Both the size of and variability in the reduction are similar to the values reported for propranolol.[8 14 20] However, the mechanisms of action of somatostatin and analogues are quite different from those of β blockers, suggesting that the variability in reduction may at least in part be due to the heterogeneous nature of cirrhotic portal hypertension; additionally, variable compliance might have had an effect. Nevertheless, unlike propranolol, octreotide consistently reduces azygos blood flow[14] and intravariceal pressure[20] more than it reduces portal pressure itself,[21] effects that could have contributed to our results.

Long term octreotide and liver function

All patients surviving the 6 months of the trial showed an improvement in liver function. However, the improvements in Child's grade and plasma concentrations of albumin, bilirubin, and alanine aminotransferase were significantly greater with combined treatment. Moreover, hepatocyte function was significantly improved with this treatment but not with sclerotherapy alone. In contrast, the circulating concentrations of alkaline phosphatase were lower with sclerotherapy alone, presumably reflecting the cholestatic effect of octreotide. Nevertheless, the results of this study suggest that octreotide improves overall hepatic function in patients with cirrhotic portal hypertension. The mechanism whereby octreotide stimulates liver function remains unclear but could be due to direct or indirect effects on hepatocytes.[22]

In this trial octreotide stimulated hepatic reticuloendothelial activity, confirming previous observations in experimental animals.[15] The phagocytic activity of the reticuloendothelial system is impaired in cirrhosis, mainly due to depression of the hepatic system, which contributes up to 80% of the total activity of the reticuloendothelial system.[23] Patients with cirrhosis who have a measurably impaired hepatic reticuloendothelial

Table 4 Changes in activity of hepatic and splenic reticuloendothelial system in patients treated with octreotide and injection sclerotherapy or sclerotherapy alone

	Octreotide and injection sclerotherapy median change (interquartile range)	Injection sclerotherapy median change (interquartile range)*	95% CI for difference between treatments	P value for difference between treatments
Activity of reticuloendothelial system (% injected dose):				
Hepatic	7.15 (5.23 to 11.90)	–1.6 (2.0 to 0.075)	6.98 to 12	< 0.0005
Splenic	3.95 (2.3 to 6.97)	1.35 (–0.05 to 1.95)	1.3 to 6.3	0.002

*Excludes 5 patients who died before end of trial.

Key messages

- The long term use of vasoactive drugs as adjuvant treatment after endoscopic sclerotherapy or ligation for acute variceal haemorrhage has been suggested to reduce the risk of variceal rebleeding
- This randomised trial found that the addition of long term octreotide to endoscopic treatment reduced the rate of recurrent variceal haemorrhage in patients with cirrhotic portal hypertension
- Octreotide also improved survival after acute variceal haemorrhage in such patients
- Long term administration of somatostatin analogues offers a promising treatment to prevent recurrent variceal haemorrhage

system have a shorter survival than those who have normal activity, in spite of similar clinical and biochemical abnormalities.[23] The reduced survival may be because clearance of endotoxin is reduced, which could contribute to liver necrosis. The clinically significant improvement in the activity of the hepatic reticuloendothelial system with combined treatment may have contributed to the improved liver function discussed.

Potential of long term somatostatin analogues

At the outset of this study there were few data on the use of somatostatin analogues in the long term management of cirrhotic portal hypertension. We therefore incorporated a detailed evaluation of the nature and severity of liver disease at the beginning and end of the trial. Furthermore, as the focus of the study was the long term prevention of variceal rebleeding, we sought patients whose condition was initially stable and who would comply with trial treatment. Nevertheless, given the positive results of this trial and the appeal of permanent pharmacological modification of portal hypertension, the administration of long term adjuvant treatment immediately after the end of the acute phase of variceal haemorrhage might be appropriate. In addition, the use of long term adjuvant treatment could be widened to include patients who have had recurrent variceal haemorrhage.

Our trial was undertaken before data became available on the relative benefits of variceal ligation over sclerotherapy.[4 5] However, variceal ligation is similar to sclerotherapy in that the underlying portal hypertension remains, so long term somatostatin analogues may be similarly beneficial after variceal ligation.

The results of this controlled trial suggest that long term octreotide, used as an adjuvant to endoscopic sclerotherapy, reduces the incidence of recurrent variceal bleeding and improves survival in cirrhotic patients. Further randomised trials are needed to confirm these effects and to compare somatostatin analogues with other drugs in the long term management of portal hypertension. The recent development of long acting slow release preparations of somatostatin analogues[24] make comparison with β blockers particularly desirable.

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Conflict of interest: Sandoz manufactures octreotide.

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Endpiece

Asherisms

It is not always worth the discomforts of major surgery to get minor recovery.

From *A Sense of Asher*, selected by Ruth Holland (BMA Publications, 1984)