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A prospective randomised controlled clinical trial comparing somatostatin and vasopressin in controlling acute variceal haemorrhage

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Abstract

Twenty two patients were entered into a randomised controlled clinical trial comparing the efficacy of somatostatin and vasopressin in controlling acute variceal haemorrhage. Somatostatin was significantly more successful in controlling acute variceal haemorrhage than vasopressin ($p=0.003$). Furthermore, no complications were observed during treatment with somatostatin.

Introduction

The main objective of vasoactive drug treatment of portal hypertension is to control variceal haemorrhage until definitive treatment can be undertaken. Although vasopressin has been used for several years for the emergency control of bleeding oesophageal varices,¹ it is successful in only about half of all patients.² Moreover, treatment with vasopressin may have undesirable side effects such as coronary vasoconstriction, pulmonary oedema, and abdominal colic.³

Somatostatin, first isolated from the hypothalamus in 1972,⁴ is widely distributed throughout the body, particularly high concentrations being found in the central nervous system, gastrointestinal tract, and pancreas. In addition to inhibiting the release of many gastrointestinal hormones,⁵⁻⁷ somatostatin is also a potent inhibitor of gastric and pancreatic secretions.^{8,9} Furthermore, studies of the effects of somatostatin on hepatic haemodynamics in animals and on wedged hepatic venous pressure in man have suggested that somatostatin may be effective in controlling acute variceal haemorrhage.^{10,11} The aim of this study was to compare the efficacy of somatostatin and vasopressin in controlling acute variceal haemorrhage in a prospective randomised controlled clinical trial.

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Methods

We studied patients with appreciable variceal haemorrhage as defined by: either systemic disturbance (pulse rate greater than 100 beats/minute, systolic blood pressure less than 100 mm Hg) for two consecutive hours necessitating blood transfusion; or necessity to transfuse two units of blood in 24 hours to maintain vital signs. Bleeding varices were confirmed by endoscopy as the source of haemorrhage in all patients.

Twenty two patients, satisfying the entry criteria, were randomly allocated (using sealed envelopes) to receive intravenously either vasopressin (argipressin; Ferring Pharmaceutical Company) or somatostatin (Serono Laboratories, UK). The cause of portal hypertension, grading of hepatic function according to Child's criteria,¹² age, sex, and ratio of index to interval episodes of bleeding were similar in the two groups (table 1). An index episode of bleeding was defined as the first variceal haemorrhage and interval episodes as all subsequent haemorrhages while the patient was undergoing maintenance sclerotherapy.

TABLE 1—Clinical features of patients with acute variceal haemorrhage receiving either vasopressin or somatostatin

	Vasopressin (n = 12)	Somatostatin (n = 10)
No with portal hypertension due to:		
Cirrhosis		
Alcohol related	6	5
Cryptogenic	3	3
Primary biliary cirrhosis	1	0
Sarcoidosis	1	0
Paroxysmal nocturnal haemoglobinuria	0	1
Extrahepatic block	1	1
No with Child's classification:		
A	2	2
B	4	2
C	6	6
Age (years):		
Mean (SEM)	51.5 (2.9)	55.8 (5.0)
Range	30-73	39-72
No of men	6	6
No of episodes of bleeding:		
Index	8	6
Interval	4	4

Patients selected to receive vasopressin were infused at a rate of 0.4 U/min for six hours. If bleeding stopped the rate of vasopressin infusion was decreased to 0.2 U/min for the following six hours, then decreased to 0.1 U/min for a further six hours, and finally stopped if no further bleeding occurred. Patients allocated to receive somatostatin received a bolus dose of 250 µg followed by a constant infusion of 250 µg/h for 24 hours. Twelve patients received vasopressin and 10 somatostatin. In 18 of the 22 patients vasopressin or somatostatin was used as a first line treatment. In the four remaining patients the varices had been injected on admission as an initial treatment but, because of continued bleeding, they were randomised to receive one or other drug (one vasopressin and three somatostatin).

Successful control of variceal haemorrhage was defined as the stopping of bleeding as evidenced by the absence of fresh blood in the nasogastric aspirate, stable packed cell volume, or absence of other overt signs of continued bleeding during the 18-24 hours of administration of the vasoactive drug. If haemorrhage was not controlled by the vasoactive drug balloon tamponade of the oesophagus was undertaken using either a Minnesota or a Sengstaken Blakemore tube.

Results

SOMATOSTATIN

The variceal haemorrhage was successfully controlled in all 10 patients receiving somatostatin (fig 1). Seven of these patients were subsequently treated with injection sclerotherapy (one to three days later) without any further episodes of bleeding. The three others, however, rebled before definitive treatment could be undertaken.

One of the patients who rebled had been randomised to receive somatostatin after a massive haematemesis following emergency sclerotherapy. The haemorrhage was successfully controlled by infusion of somatostatin, but he rebled on two further occasions after the infusion of somatostatin had been stopped. In both cases infusion of somatostatin was again successful in controlling the variceal bleeding. He subsequently underwent successful oesophageal tran-

section using a stapling technique. Another of the three to rebled refused injection sclerotherapy after initial control of her variceal haemorrhage by somatostatin. She experienced four further appreciable episodes of bleeding in the three weeks after her initial episode, all of which were controlled successfully by a 24 hour infusion of somatostatin. She eventually died from multiple organ failure. The third patient to rebled did so after initial emergency injection sclerotherapy for acute variceal haemorrhage. The bleeding was successfully controlled by the administration of somatostatin, but she subsequently sustained further massive variceal haemorrhage, which was again controlled by somatostatin administration. She underwent oesophageal transection under somatostatin cover but subsequently died from a cardiac arrest in the intensive care unit. It should be pointed out that she had had a cardiac arrest three hours after admission with the initial episode of bleeding.

No complications were observed in any of the 10 patients during infusion of somatostatin.

FIG 1—Outcome of treatment with somatostatin in patients with acute variceal haemorrhage.

VASOPRESSIN

Variceal haemorrhage was successfully controlled by vasopressin in four of the 12 patients (one with Child's grade A hepatic function, two with Child's grade B, and one with Child's grade C), but treatment was unsuccessful in the remaining eight (fig 2). In two patients

FIG 2—Outcome of treatment with vasopressin in patients with acute variceal haemorrhage.

administration of vasopressin had to be stopped despite continued active bleeding from the varices because of undesirable side effects (pulmonary oedema in one, chest pain and abdominal colic in the other). Haemorrhage was eventually controlled in these two patients by balloon tamponade.

Balloon tamponade was carried out in the six remaining patients in whom vasopressin failed to control the variceal haemorrhage. In four the variceal haemorrhage was eventually controlled by the

combination of balloon tamponade and vasopressin, but two of these patients died from direct complications of balloon tamponade (inhalation in one case, oesophageal ulceration and perforation in the other). In the two remaining patients the variceal haemorrhage was not controlled by vasopressin and balloon tamponade. One of these two underwent emergency oesophageal transection but died of liver failure one week later. The other died of a combination of hypovolaemic shock and liver failure before any further treatment could be undertaken.

COMPARISON

Analysis of the results by Fisher's exact test (table II) showed that somatostatin was successful in a significantly greater number of patients than vasopressin in controlling acute variceal haemorrhage ($p=0.003$). When the number of episodes of bleeding controlled by somatostatin (17) was compared with the number controlled by vasopressin (four) the difference between the treatments was of even greater significance ($p=0.0002$).

TABLE II—Results of vasopressin and somatostatin treatment in controlling acute variceal haemorrhage. Figures indicate numbers of patients in whom treatment was successful or unsuccessful with numbers of episodes of bleeding in parentheses

	Successful	Not successful
Vasopressin (n = 12)	4	8
Somatostatin (n = 10)	10 (17)	0

$p=0.003$ (0.0002), Fisher's exact test.

Discussion

The results of this randomised controlled clinical trial suggest that somatostatin is more successful than vasopressin in controlling acute variceal haemorrhage when success is defined as the stopping of bleeding during the administration of the vasoactive drug. Moreover, no complications were observed in those patients who received somatostatin. Although we initially intended to randomise 30 patients to receive either somatostatin or vasopressin, an adverse report¹³ prompted us to perform a preliminary analysis of our data. The highly significant result obtained ($p=0.003$) in the first 22 patients clearly indicated that the trial should be stopped.

This paper describes the first full report of a randomised clinical trial comparing the efficacy of somatostatin and vasopressin in controlling acute variceal haemorrhage. These results agree with two previous reports, one of which is anecdotal,¹¹ the other reported in abstract form only.¹⁴ Raptis and Zoupas, however, in a study of only five patients found that somatostatin had no beneficial effect in the control of acute variceal haemorrhage.¹⁵ The reason for the difference in results is difficult to explain. In our experience, success with the administration of somatostatin demands scrupulous attention to detail. The bolus injection must be given after the infusion has been started, and there must be no delay in changing infusion bags. Although Raptis and Zoupas gave a bolus injection followed by a constant infusion for up to 74 hours, they do not give any precise details of their methods of administration or any indication of the precautions they took to ensure that the circulating concentrations of the hormone did not fall to below that required to exert a therapeutic effect.¹⁵ Furthermore, their failure to show a fall in portal pressure after administration of somatostatin at operation is contrary to observations in cirrhotic rats¹⁶ and cirrhotic patients,¹⁷ using roughly the same dose of somatostatin. Their failure to show a beneficial effect of somatostatin in the management of acute variceal haemorrhage may have been related to the method of administration.

Somatostatin has been shown to reduce splanchnic blood flow in experimental animals^{18,19} and in man.¹¹ On the basis of

these initial studies and the observation that somatostatin lowers wedged hepatic venous pressure in patients with cirrhosis the hormone was suggested to be of possible value in the management of patients presenting with acute variceal haemorrhage.¹¹ Reports on the effects of somatostatin on hepatic haemodynamics in cirrhosis have, however, been contradictory. Thus an infusion of somatostatin ($1 \mu\text{g/kg}$ body weight/min) has been reported to reduce wedged hepatic venous pressure in man.¹¹ Similarly, Bosch *et al* observed that an injection ($1 \mu\text{g/kg}$ body weight) or an infusion ($7.5 \mu\text{g/min}$) of somatostatin significantly decreased both wedged hepatic venous pressure and estimated liver blood flow in cirrhotic patients.¹⁷ In contrast, Sonnenberg *et al* reported that an infusion of somatostatin $250 \mu\text{g/h}$ had no effect on wedged hepatic venous pressure or liver blood flow in cirrhotic patients.¹⁹ The rate of infusion of somatostatin used by Sonnenberg *et al* ($3.0 \mu\text{g/kg}$ body weight/h) was lower than that used in other clinical studies and roughly midway between the rates of infusion of the hormone that either have had no effect or have significantly lowered portal pressure in cirrhotic rats.¹⁶ Furthermore, we have previously shown that in cirrhotic rats the beneficial effects of an infusion of somatostatin on hepatic haemodynamics are enhanced by prior bolus administration of the hormone.¹⁸ It therefore seems likely that the conflicting reports on the effects of somatostatin on hepatic haemodynamics in cirrhotic patients may be related to the amount given and the mode of administration.

The precise mode of action of somatostatin has not yet been established. The rapidity of onset of its effects on hepatic haemodynamics in experimental animals and in man suggests that the peptide acts directly on the smooth muscle of the splanchnic blood vessels.¹⁰

Although bleeding stopped during the infusion of somatostatin in all 10 patients, three of the patients rebled before definitive treatment (either the first injection of sclerosant into the varices or oesophageal transection) could be implemented. These episodes of rebleeding were, however, controlled with further infusions of somatostatin, suggesting that a more prolonged infusion of the hormone may be necessary to reduce further the risk of haemorrhage before definitive treatment is carried out. Prolonged use of somatostatin alone may therefore avoid the use of balloon tamponade with all its recognised risks such as oesophagitis, rupture of oesophagus, aspiration pneumonia, and airway obstruction. The 25% mortality directly attributable to balloon tamponade in this study is similar to that previously reported.²⁰

In addition, somatostatin has several other potential advantages over vasopressin in the management of bleeding oesophageal varices. Firstly, as somatostatin has been shown to stop bleeding from peptic ulcer in about 80% of patients presenting for treatment²¹ the hormone will have the additional benefit of controlling haemorrhage from other sources when they coexist with oesophageal varices. Secondly, somatostatin has been shown to be effective in controlling haemorrhage from ulcerative oesophagitis, a condition that sometimes accompanies bleeding oesophageal varices.²² Finally, somatostatin, by inhibiting gastric acid secretion,⁸ may promote healing by preventing clot dissolution.

In conclusion, somatostatin would appear to be more effective than vasopressin in controlling acute variceal haemorrhage. Furthermore, in both the present study and studies by other workers²¹ administration of somatostatin has appeared to be free from the complications observed during administration of vasopressin. It therefore appears that somatostatin is an effective stopgap measure, giving time for patients' conditions to improve and diagnostic measures to be undertaken.

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ADDENDUM—Since this paper was accepted for publication a report of a prospective randomised clinical trial comparing the effects of somatostatin and vasopressin in the control of acute variceal haemorrhage has been published (Kravetz D, Bosch J, Teres J, Bruix J, Rimola A, Rodes J. Comparison of intravenous somatostatin and vasopressin infusion in the treatment of acute variceal haemorrhage. *Hepatology* 1984;4:442-6). There was no difference in the effectiveness of somatostatin and vasopressin in controlling variceal haemorrhage, but administration of somatostatin was associated with fewer complications. The two trials are not, however, strictly comparable because of differences, to which we have drawn attention (*Hepatology*, in press), in the mode of administration of somatostatin and vasopressin.

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Height at diagnosis of diabetes in children: a study in identical twins

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Abstract

The height at diagnosis of 16 insulin dependent diabetics aged under 19 was compared with that of their unaffected identical cotwins measured at the same time. In eight pairs the diabetic was shorter, and in the remainder the cotwins were the same height. In those diabetics who were shorter than their cotwins at diagnosis the average period of growth delay before diagnosis was at least 35 weeks; by contrast, the mean duration of symptoms was only six weeks. No cause for the growth delay other than the diabetes was known in any of the twins.

These findings show that the onset of insulin dependent diabetes may be a slow process, with growth delay occurring several months before symptoms appear.

Introduction

Growth is a sensitive indicator of health in childhood. Uncontrolled diabetes retards growth: before the discovery of insulin growth stopped completely in children who developed diabetes.¹ We have used these observations to determine whether diabetes can be present, as shown by growth delay, before the appearance of symptoms.

Studies of heights at diagnosis in diabetic children have produced conflicting results. In most the diabetics were found to be taller than expected,²⁻⁹ although some studies showed that their heights were normal^{8,10,11} or that they were shorter.¹²⁻¹⁴ These discrepancies may be due to the difficulty in obtaining exactly matched control groups. When comparing heights the groups must be accurately matched for social class, racial origin, and parental height. The ideal control for a diabetic child is his unaffected identical twin, as twins usually grow at the same rate and to the same final height.¹⁵

We studied the heights of identical twins discordant for insulin dependent diabetes at the time of diagnosis of the diabetic twin in order (a) to determine whether the diabetic was taller or shorter at diagnosis than his unaffected cotwin and (b), if there was a difference, to estimate how long before diagnosis growth had been affected.

Subjects and methods

We studied identical twins included in the King's College Hospital survey. Monozygosity was established as described.¹⁶

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