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Somatostatin in the treatment of acute pancreatitis: a prospective randomised controlled trial

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SUMMARY **A prospective study was carried out to evaluate the efficacy of somatostatin in the treatment of acute pancreatitis. Seventy one patients were randomised to control (h=36), or to the somatostatin group (h=35) who received somatostatin 100 μg/h after a 250 μg bolus for the first two days. The following were compared in the two groups on admission and two days later: laboratory tests of prognostic significance, severity of pancreatitis, and also morbidity and mortality. Of the nine laboratory tests compared, the white blood cell count, lactate dehydrogenase, and urea concentrations were significantly lower in the somatostatin group two days after admission. Severity of pancreatitis after hospitalisation increased in fewer patients given somatostatin (NS). There was a trend toward fewer complications, especially local, in the somatostatin group. Mortality in both groups was low. Somatostatin appeared to reduce the local complications of acute pancreatitis. A larger trial is necessary to show its beneficial effect conclusively.**

Somatostatin is a hormone which suppresses pancreatic exocrine function in animals and man. The action is direct by suppressing glandular secretion as well as indirect by suppressing the secretion of gastrointestinal hormones.[1-3] In acute pancreatitis, there is intraglandular activation of digestive enzymes causing glandular destruction and release of these enzymes into the general circulation giving rise to systemic manifestations of organ failure. Theoretically somatostatin, because it suppresses pancreatic enzyme secretion, should exert a beneficial effect on acute pancreatitis.

In animals, somatostatin has been shown to prevent experimentally induced pancreatitis and to lower the mortality of established pancreatitis.[4-6] In human acute pancreatitis, there have been very few clinical studies and the results published have been inconsistent.[7,8] We have undertaken a study using somatostatin in the treatment of acute pancreatitis in the last two years and the results are presented here.

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Methods

PATIENTS

This is a prospectively randomised controlled trial conducted on patients admitted to the Department of Surgery, University of Hong Kong at the Queen Mary Hospital with a clinical diagnosis of acute pancreatitis between July 1986 and January 1988. The diagnosis is established by a serum amylase concentration of over 400 IU/l (normal <75 IU/l) and the presence of abdominal pain. Patients with acute pancreatitis caused by trauma, endoscopic intubation or division of the papilla, surgery or neoplasm of the pancreas were excluded. All patients were treated by the same conservative regimen of nil by mouth, nasogastric tube suction, intravenous fluid and cephoperazone 1 g iv every 12 hours for five days. Those patients randomised to the somatostatin group also received an intravenous bolus of somatostatin (Serono Company, Freiberg) 250 μg followed by 100 μg/h given continuously by an infusion pump for 48 hours. Somatostatin was started immediately after the diagnosis was made. Randomisation was done by drawing sealed envelopes. Informed consent was obtained from all patients.

On admission the following blood tests were

obtained: complete blood picture, electrolytes, urea, creatinine, glucose, lactic dehydrogenase (LDH), albumin, calcium, liver function tests and arterial blood gases. A similar set of blood tests was obtained two days later and at more frequent intervals if deemed necessary. Ultrasonic examination of the abdomen was done on all patients during the acute stage. In addition, serial computed tomography scans were carried out on patients if an abdominal or pancreatic mass was detected, if there was persistent fever or leucocytosis suggestive of pancreatic abscess, or if the patients' condition did not improve after three or four days of conservative treatment. Surgery was not done unless complications necessitating operative intervention developed. Endoscopic retrograde cholangiopancreatography was performed on all patients immediately after recovery from pancreatitis. Early cholecystectomy was offered to patients who had gall stones.

The following parameters of the control and somatostatin groups were compared: (1) the value of the laboratory tests at admission and at two days after admission, (2) the severity of pancreatitis as assessed according to the criteria of Imrie *et al*[9 10] at admission and at two days after admission, (3) the mortality, and (4) the incidence and type of complications. The laboratory tests to be compared were determined by Blamey *et al*[11] to be of prognostic significance. The modified Imrie's criteria[10] was used to assess severity. In this modification, the age factor (age >55) was omitted as felt that this was more appropriate as the average age of our patients was over 55 years. The list of criteria used is shown in Table 1. Patients having three or more of the poor prognosticating factors were assessed to have severe pancreatitis, while those having two or less factors were assessed to have mild pancreatitis. The Mann-Whitney and the χ^2 test were used in statistical comparisons.

Table 1 *Prognostic factors*

Oxygen (PaO_2)	<60 mmHg
Urea	>16 mmol/l
White blood cell count	$>15\times10^9$/l
Glucose	>10 mmol/l
Calcium	<2 mmol/l
Albumin	<32 g/l
SGOT	>200 IU/l
Lactate dehydrogenase	>600 IU/l

Three or more factors positive=severe acute pancreatitis.

Table 2

	Control group	*Somatostation group*
n	36	35
Age (yr)	62·6	59·7
Men (n)	17	15
Women (n)	18	21
Gall stones (n)	19	18

Table 3 *Aetiology of acute pancreatitis*

Gall stones	37
Alcohol	11
Ascaris	1
Unknown	22

Results

Seventy one patients were included in the study of which 36 were randomised to the control group and 35 to the somatostatin group. The age and sex of the two groups were similar (Table 2). The cause of pancreatitis in all patients is shown in Table 3. The incidence of gall stones in the control and somatostatin groups was similar (Table 2).

The results of the laboratory tests are shown in Table 4. Overall, the results of 3·6% of the tests were not available mostly because of handling errors. There was no significant difference in any of the tests in the control and somatostatin groups at the time of hospital admission. White blood cell count, urea and LDH concentrations were significantly lower in the somatostatin group when compared with the control group at two days after admission. The most significant difference was found in the LDH level.

Six of the patients in the control group and nine of the patients in the somatostatin group were assessed to have severe pancreatitis at admission. At two days after admission, eight patients in the control group had severe pancreatitis including three patients who were initially so assessed and five patients who deteriorated during the interval. At two days after admission, five patients in the somatostatin group had severe pancreatitis including four initially so assessed and one who deteriorated. The number of patients who deteriorated after admission was less in the somatostatin group.

Two patients in the control group and one patient in the somatostatin group died. One death in each group was the result of multiorgan failure. One patient in the control group developed cholangitic liver abscess. He refused drainage of the abscess and died of sepsis after 18 days of antibiotic treatment. Two of the deaths occurred in patients assessed to have severe pancreatitis at admission and one death occurred in patients whose pancreatitis deteriorated in the first two days.

The list of complications is shown in Table 5. The incidence of complications was lower in the somatostatin group. Pancreatic phlegmon was defined as

Table 4 *Laboratory tests*

		Control group	*Somatostatin group*	
n		36	35	p
Age	yr	62·57 (13·20)	59·74 (21·86)	NS
WBC	10^9/l	14·67 (7·22)	13·97 (6·73)	NS
WBC 2*		12·71 (6·45)	9·45 (4·06)	0·0329
Amylase	IU/l	875 (395)	1069 (487)	NS
Amylase 2		170 (216)	138 (123)	NS
SGOT	IU/l	206 (251)	219 (371)	NS
SGOT 2		51 (48)	61 (78)	NS
LDH	IU/l	361 (265)	386 (345)	NS
LDH 2		311 (150)	216 (107)	0·0088
Urea	mmol/l	6·17 (2·23)	6·33 (2·71)	NS
Urea 2		5·64 (4·24)	4·27(3·27)	0·0338
Glucose	mmol/l	8·70 (6·02)	7·62 (2·71)	NS
Glucose 2		6·88 (2·59)	7·65 (2·52)	NS
Calcium	mmol/l	2·16 (0·21)	2·14 (0·20)	NS
Calcium 2		2·02 (0·18)	1·97 (0·16)	NS
Albumen	mmol/l	43·30 (5·23)	42·40 (6·93)	NS
Albumen 2		36·75 (5·48)	36·29 (5·58)	NS
PaO_2	mmHg	61·97 (17·46)	68·22 (17·80)	NS
PaO_2 2		63·78 (14·98)	68·90 (21·16)	NS

*WBC 2 WBC at two days after admission.
( ) standard deviation.

swelling of the pancreas together with peripancreatic inflamation and collections of fluid as shown by computed tomography scan. Each of the patients developing a pancreatic phlegmon had a hospital stay of more than 14 days (maximum 60 days). The control group appeared to have a higher incidence of local complications (pancreatic abscess, pseudocyst and phlegmon) compared with the somatostatin group. Upper gastrointestinal bleeding was defined as the aspiration of coffee ground material or blood from the nasogastric tube together with a recorded drop in haemoglobin level. The incidence of acute upper gastrointestinal bleeding was lower in the somatostatin group. All patients developing upper gastrointestinal bleeding underwent upper endoscopy. One patient in the control group had an acute duodenal ulcer. Gastritis with or without superficial erosions was found in the other patients. The bleeding in all patients subsided with ranitidine treatment.

Table 5 *Complications*

Complication	*Control group (n)*	*Somatostatin group (n)*
Pseudocyst	1	1
Pancreatic abscess	1	0
Inflammatory pancreatic swelling	6	2
Upper gastrointestinal haemorrhage	3	1
Liver abscess	1	0
Multiorgan failure	1	1
	13	5

Discussion

There is no accepted drug treatment for acute pancreatitis. Glucagon which suppress pancreatic secretion and aprotinin which inactivates pancreatic enzymes have been studied, but no improvement in survival has been shown with any treatment.[9 12 13] Somatostatin is a potent inhibitor of pancreatic exocrine secretion. In animal studies, it has been shown to prevent experimentally induced pancreatitis, as well as reducing the severity and decreasing the mortality of established acute pancreatitis.[4–6] There are only two reports on the use of somatostatin to treat acute pancreatitis in man. Limberg and Kommerell reported subjective clinical improvement and a rapid fall of serum enzyme concentrations in an uncontrolled study.[7] Usadel *et al* reported no advantage using somatostatin in a double blind trial.[8] We feel that further studies are warranted because of the good results obtained in animal studies.

The dosage of somatostatin at 1·35 μg/kg/h has been found to suppress pancreatic enzyme secretion by 76·7%.[12] Another study reported inhibition of pancreatic secretion by 40% using a 3 μg/h infusion and maximal inhibition was attained at a rate of 90 μg/h.[14] The dosage of somatostatin used in this study was probably adequate as it was equivalent to 1·75 μg/kg/h or more in the majority of the patients. The duration of treatment may be insufficient for some patients. The serum amylase concentration was seen to rise after somatostatin was stopped in a few patients.

The laboratory tests compared, except for the serum amylase concentration, have been found to be of prognostic significance.[11] A drop in the serum amylase concentration occurred in the control and somatostatin groups. Even though the drop was larger in the somatostatin group, the difference was not statistically significant. Somatostatin treatment also did not result in any significant changes in the serum glucose, calcium, and albumin concentrations.

Pulmonary oedema, congestion and effusion occur frequently in acute pancreatitis[15] leading to impaired arterial blood oxygenation. No difference was found in the arterial PO_2 levels after somatostatin administration. This indicated that the pulmonary damage was not improved. The serum SGOT concentrations were not different indicating that the degree of liver impairment, which is also seen in acute pancreatitis, was unchanged with somatostatin treatment.

There was a small but significant decrease in the level of serum urea with somatostatin treatment which may indicate some improvement in renal function.

The serum LDH concentration is a measurement of the amount of tissue destruction and in acute pancreatitis, is indicative of the amount of pancreatic and peripancreatic inflamation and necrosis. The LDH was significantly lower in the somatostatin group when compared with the control group at two days after hospitalisation. We further analysed the change in serum LDH levels occurring in the first two days. Six patients in the control group and nine patients in the somatostatin group had raised LDH at admission. At two days after admission, eight patients in the control group had raised LDH including three who initially had raised concentrations, and five in whom the LDH rose. At two days after admission, five patients in the somatostatin group had raised LDH including four patients who initially had raised concentrations and one in whom the LDH rose. Our interpretation of these findings was that local inflamation and necrosis, especially if it has not already started, was suppressed by somatostatin treatment. The significantly lower WBC in the somatostatin group after treatment can also be explained by the suppression of local reaction.

The incidence of local complications including the formation of pseudocyst, abscess, or pancreatic phlegmon was lower in the somatostatin group. This finding appeared to support our LDH data interpretation. We further analyse the relationship between the rise of serum LDH concentrations after hospitalisation and the development of local pancreatic complications. Altogether 11 patients in the entire study develop local complications (eight in the control group and three in the somatostatin group). Of these, nine patients had, at two days after admission, either a rise in the serum LDH concentrations from being initially normal, or a further rise from an already raised concentration. Of the 61 patients who had no local pancreatic complications, only five registered such a rise. Thus, there was a significant correlation between rise in the serum LDH concentrations after hospitalisation and the development of local pancreatic complications (χ^2= 31·7 by χ^2 test). Somatostatin administration appeared to reduce this tendency.

The incidence of upper gastrointestinal haemorrhage was lower in the somatostatin group. The numbers were, however, too small to be significant. Somatostatin effectively inhibits basal and stimulated gastric acid output.[16,17] This may inhibit stress peptic ulcer or gastritis formation which frequently occurs with severe pancreatitis.[18,19]

Prognosticating factors have been used in the prediction of the severity of pancreatitis. The modified Imrei's criteria were used in this study and appeared to reflect the true severity as all three deaths occurred in patients predicted to have severe pancreatitis. The number of patients whose pancreatitis increased in severity in the first two days in the somatostatin group (one patient) was less when compared with the control group (five patients). Because of the small number of patients, however, the difference was not statistically significant.

Somatostatin did not seem to have any effect on the mortality of acute pancreatitis. From the previous analysis, the effect of somatostatin is mainly local. The systemic manifestations of pancreatitis are not influenced. Mortality of acute pancreatitis has been shown to be the result of a combination of three factors: local complications, systemic side effects and exacerbation of pre-existing illnesses.[15,20] Having a beneficial effect on one factor will not significantly change the mortality especially if the mortality is intrinsically low.

Somatostatin does seem to have a beneficial local effect. The question arises as to how can this be applied in the treatment of pancreatitis. The candidates for somatostatin therapy are those who develop local complications but the best timing is before the onset of these complications. In localities with a high incidence of pancreatic pseudocysts, abscesses or necrosis, somatostatin should be started as soon as possible on all patients. Optimally, somatostatin should only be given to patients prone to develop these complications. At present, we are in the process of reviewing the clinical parameters of patients suffering from acute pancreatitis in order to identify those associated with the development of complications. A further trial with somatostatin will be carried out on patients assessed to have a high risk of developing complications.

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