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Octreotide 24-h prophylaxis in patients at high risk for post-ERCP pancreatitis: results of a multicenter, randomized, controlled trial

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SUMMARY

Background: Pharmacological prophylaxis of post-ERCP pancreatitis is costly and not useful in most non-selected patients, in whom the incidence of pancreatitis is 5% or less. However, it could be useful and probably cost-effective, in patients at high risk for this complication, where the post-procedure pancreatitis rate is 10% and more.

Aim: To assess the efficacy of octreotide in reducing the incidence and severity of post-ERCP pancreatitis and procedure-related hospital stay, in subjects with known patient-related risk factors.

Methods: A total of 120 patients were randomly allocated to receive octreotide or not, in a multicentre, randomized, controlled trial. The drug was given subcutaneously, 200 μg t.d.s., starting 24 h before the ERCP procedure, in patients with either sphincter of Oddi dysfunction, or a history of relapsing pancreatitis or post-ERCP pancreatitis, or who were aged under 35 years, or who had a small common bile duct diameter (< 8 mm).

Results: A total of 114 patients (58 in the octreotide group and 56 in the control group) completed the trial. Post-procedure pancreatitis occurred in seven octreotide-treated patients (12.0%) and eight controls (14.3%). The two groups showed no significant differences in the incidence or severity of pancreatitis. Twenty-four hours after the procedure, severe hyperamylasemia (more than five times the upper normal limit) without pancreatic-like pain was recorded in three octreotide-treated patients (5.2%) and six controls (10.7%), the difference being not significant.

Conclusion: Twenty-four-hour prophylaxis with octreotide proved ineffective in preventing post-ERCP pancreatitis and in avoiding 24-h severe hyperamylasemia in high-risk patients.

INTRODUCTION

The main questions still debated relating to the diagnostic and therapeutic endoscopic procedures involving Vater's papilla (ERCP) are post-procedure pancreatitis and its prevention.

Acute post-ERCP pancreatitis is still the most frequent and feared complication. A recent review of prospective series found a mean prevalence of 5.2% after diagnostic procedures and 4.1% after therapeutic procedures.[1] However, in recent prospective studies in non-selected cases the rate of this complication has been reported to range widely, from 1.3% to 7.6%.[2–9] The varying

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incidence of post-ERCP pancreatitis very likely reflects differences either in the definitions of pancreatitis or in patient populations. In fact, the incidence seems to correlate with the percentage of patients at high risk for this complication included in the studies, being higher in those series with a larger number of patient- and technique-related risk factors.[5, 8] Although in non-selected cases the incidence ranges from 1 to 6%, it can rise to 12–31% in high-risk cases.[5, 7–12]

Pharmacological prevention of pancreatitis after ERCP or sphincterotomy has been widely investigated in recent years but still remains debated. A number of drugs have been tested, mainly antisecretory or anti-protease agents, or corticosteroids, administered either before or during the procedure, or in the post-procedural period, but results are conflicting.[13, 14] Somatostatin and gabexate mesilate have proved effective but require continuous intravenous infusion and therefore a prolonged hospital stay. Octreotide is the simplest and cheapest agent and does not require prolonged administration in the post-procedural period. However, a single bolus immediately before and 1 hour after the endoscopic procedure has proved ineffective, although prolonged administration of the peptide before the procedure significantly lowered the 24-h post-procedural amylase curve.[15–18]

A large number of patients need to be treated to prevent a very small number of cases of post-ERCP pancreatitis in clinical practice, Therefore, pharmacological prophylaxis does not appear to be useful in most cases and it is expensive if routinely performed in all patients. In contrast, a pharmacological prophylaxis given only to patients at high risk for post-procedure pancreatitis could, if useful, be cost-effective.

The present study was therefore designed to establish whether 24-h prophylaxis with octreotide, before ERCP or biliary sphincterotomy in patients at high risk for post-ERCP pancreatitis, significantly reduced either the incidence and severity of the complication, or the procedure-related length of hospital stay.

MATERIALS AND METHODS

A total of 120 consecutive hospitalized patients (49 males and 71 females; age range 19–85 years, mean age 51.8 years) with known patient-related risk factors for post-ERCP pancreatitis, who were scheduled to undergo diagnostic ERCP or endoscopic biliary sphincterotomy (when indicated), were randomly allocated to receive either pharmacological prophylaxis (60 cases) or no treatment (60 cases) in a prospective, controlled multicentre trial conducted in 10 centres over a 24-month period. All 10 centres were secondary referral centres with a large volume of cases; all endoscopists involved in the study currently perform more than 100 endoscopic biliopancreatic procedures every year, and have been doing so for since at least 10 years.

The primary end-point of the study was to detect any reduction in the incidence and severity of post-procedure pancreatitis. The secondary end-point was to look for any difference between the treated and control groups with regard to the length of hospital stay or potential same-day discharge.

Written informed consent was obtained from all patients for the endoscopic procedure and data management; informed consent for prophylaxis was also obtained from all patients in the treated group before study entry. The study was approved by the ethics committee at each centre.

Criteria for exclusion were: choledochoduodenal anastomosis separating the main pancreatic duct orifice from the area of the intervention; previous papillosphincterotomy; clinical/morphological evidence of chronic pancreatitis or pancreatic insufficiency; pancreatic or Vater's papilla cancer; renal failure; diabetes and; acute pancreatitis at the time of the endoscopic procedure. Subjects aged < 18, pregnant women, breast-feeding mothers, patients with a history of alcohol abuse and those who refused to consent to the study were also excluded.

Study design

A power analysis was conducted for detecting differences at the 5% level of significance between a group with a 15% rate of post-procedure pancreatitis and a group with a 2% rate, as reported in the literature for high-risk and non-selected patients, respectively. It was found that a sample size of 60 cases in each arm would provide a power of 80%.

Random numbers assigning patients to the treatment or control group were given by an independent statistician. Twelve patients were assigned to each centre, six in the control and six in the treatment group. Endoscopists who performed the procedure were unaware of the treatment classification.

Overall, 60 patients were randomly allocated to receive a 24-h, four-dose pre-treatment with 200 μg of octre-

otide subcutaneously (08.00 hours, 16.00 hours, 00.00 hours the day before the procedure, and 08.00 hours on the day of the procedure). Sixty patients received no pharmacological treatment. In the treatment group procedures were performed at least 1 h after the last octreotide dose.

All patients stayed in hospital for a 48-h follow-up after the procedure. Patients with pancreatic drainage or stenting were excluded from the study.

Concomitant therapy with aprotinin, somatostatin and gabexate mesilate was a reason for exclusion, but analgesics and sedatives were allowed.

Serum amylase was measured and white blood cells were counted in blood drawn before the procedure and after 2, 4–6 and 24 h. Hyperamylasemia was defined as an increase to above the upper limit of normal, in a patient with normal basal levels. Leucocytosis was defined as a white cell count > 10 000 cells/mm^3.

Pancreatic-like pain, defined as persistent epigastric pain, often irradiating to the back, was recorded before the procedure, and 2, 4–6 and 24 h after.

Ultrasonography was performed in cases with 24-h hyperamylasemia more than five times the normal upper limit, and/or pain; cases in whom pancreatic focal necrosis and pancreatic or peripancreatic fluid collections were suspected on ultrasonographic examination, also underwent abdominal computed tomography (CT scan).

Patients with either 24-h pancreatic-like pain and hyperamylasemia, or hyperamylasemia more than five times the normal upper limit without pancreatic-like pain underwent an additional 48-h serum amylase assay and pain recording.

Patients with post-ERCP pancreatitis were followed until recovery from the complication.

Patients were evaluated in the post-procedure period as follows: (a) 4–6 h after the procedure for pancreatic-like pain or for hyperamylasemia more than five times the normal upper limit, or both; (b) 24 h after the procedure for hyperamylasemia more than five times the normal upper limit, irrespective of pancreatic pain or leucocytosis, and for acute pancreatitis.

Same-day discharge was considered when 4–6 h after the procedure patients had neither pain nor hyperamylasemia more than five times the normal upper limit.[19, 20] Discharge 24 h after the procedure was considered when at this time patients had neither pain nor serum amylase more than five times the normal upper limit. Discharge 48 h after the procedure was considered for cases without post-procedure pancreatitis and for those with 24-h hyperamylasemia more than five times the normal upper limit, irrespective of pancreatic-like pain. In cases with pancreatitis but no local or systemic complications, discharge from hospital was planned when patients reported no pancreatic-like pain and when serum amylase levels were lower than five times the normal upper limit.

Definition of patient-related risk factors for post-ERCP pancreatitis

We considered the following patient-related factors to be associated with a higher risk of post-ERCP pancreatitis: (i) age between 18 and 35 years;[5, 8] (ii) history of relapsing pancreatitis of whatever aetiology, defined as more than two episodes of hyperamylasemia, with pancreatic-like pain, in the 6 months before the endoscopic procedure;[5, 10] (iii) previous episode of post-ERCP pancreatitis, defined as persisting 24-h post-procedure pancreatic-like pain, with at least a threefold increase in serum amylase;[10, 21, 22] (iv) sphincter of Oddi dysfunction, biliary and pancreatic type, defined on the basis of the Milwaukee and Indianapolis classifications, respectively, and diagnosed on the basis of radiological and clinical findings in type 1 dysfunction, confirmed by manometric investigation in types 2 and 3;[1, 2, 4, 5, 7, 11, 23, 24] (v) common bile duct diameter < 8 mm, although opinions are still conflicting about the increased risk for post-procedure pancreatitis with a non-dilated duct.[2, 4, 5, 25, 26]

Patient-related risk factors for both groups are reported in Table 1.

Definition of pancreatitis

Clinical features considered indicative of acute pancreatitis were pancreatic-like pain persisting for at least 24 h after the procedure, with serum amylase more than five times the normal upper limit, with or without leucocytosis. Although the combination of pain and amylase more than three times the normal upper limit has been suggested as an indicator of pancreatitis, we used a 24-h fivefold increase in serum amylase associated with pancreatic-like pain.[8, 22] In our own experience and that of other centres participating in the trial, only among those cases did pain and/or hyperamylasemia still persist 48 h after the procedure, and CT scan findings were consistent with pancreatitis.[27]

Table 1. Patient-related risk factors: numbers and percentages of cases

	Octreotide *n* cases (%)	Control *n* cases (%)
Age between 18 and 35 years	17 (28.3%)	12 (20.0%)
History of relapsing pancreatitis	11 (18.3%)	15 (25.0%)
Previous post-ERCP pancreatitis	2 (3.3%)	5 (8.3%)
Sphincter of Oddi dysfunction	13 (21.7%)	14 (23.3%)
Common bile duct diameter < 8 mm	44 (73.3%)	36 (60.0%)
More than one risk factor	25 (41.7%)	22 (346.7%)

The severity of pancreatitis was classified either using Atlanta criteria or on the basis of the hospital stay (2–3 days, mild; 4–10 days, moderate; more than 10 days or complications, severe).[22, 28]

Endoscopic procedure

After overnight fasting, patients were given standard pre-medication followed by broad-spectrum antibiotics for 24 h after the procedure. For duct opacification, iopamidol was injected (Iopamir, Bracco, Milan), a low-osmolality, non-ionic contrast medium. Patients took no food for at least 12 h after the procedure. Stones were cleared either by spontaneous passage or by mechanical extraction (balloon or Dormia basket). Naso-biliary drainage was positioned in cases in which residual lithiasis was suspected or in cases with acute cholangitis. For each procedure, we recorded patients' clinical characteristics (demographics, reasons for endoscopic examination, indication to procedure), anatomical aspects (major papilla, descending duodenum, biliary tree and pancreatic ductal system), pancreatic duct opacification, pre-cut technique, other endoscopic manoeuvres and 48-h outcome.

Statistical analysis

The independent associations of each of the dichotomous variables, presence of pancreatic-like pain and hyperamylasemia more than five times the normal upper limit, with treatment group, were assessed by the χ^2-test, with Yate's correction for continuity.

RESULTS

The characteristics of the patients and procedures for both groups are reported in Table 2. Six patients, two in the treatment group and four in the control group, were excluded from the final evaluation for the following reasons: the examination was not carried out (one case in the control group, due to severe cardiac bradiarrhythmia); the medication was discontinued because of an allergic reaction (one case in the treatment group); the data were not complete (one case in the treatment group and three controls).

Data analysis was done for 58 patients in the treatment group and 56 controls. In all these patients either diagnostic or therapeutic endoscopic procedures were successful.

All patients with sphincter of Oddi dysfunction (13 in the octreotide group and 14 controls) had type 1 dysfunction and underwent biliary sphincterotomy without manometric investigation; in no cases was prophylactic short-term pancreatic stenting performed after sphincterotomy.

Pancreatic duct injection was obtained in 35 out of 58 cases (60.3%) and 39 out of 56 cases (69.6%) in the octreotide and control groups, respectively. The difference is not significant. Difficult cannulation, defined as multiple pancreatic duct injection, pre-cut technique, or guide-wire biliary cannulation, was reported in 14 out of 58 cases (24.1%) in the octreotide group and 23 out of 56 (41.1%) in the control group. Although remarkable, the difference is not significant.

Table 3 reports numbers and percentages of patients with hyperamylasemia more than five times the normal upper limit, and pancreatic-like pain, recorded 2, 4–6 and 24 h after the endoscopic procedure.

Table 2. Characteristics of patients and endoscopic procedures

	Octreotide	Control
Number of cases	60	60
Male/Female	20/40	29/31
Mean age (years)	51.2	52.3
Age range (years)	22–85	19–83
Drop-outs (*n*)	2	4
Endoscopic biliary sphincterotomy (*n*)	40	43
Pre-cut technique (*n*)	2	1
Diagnostic ERCP (*n*)	16	12
Naso-biliary drainage (*n*)	13	9
No pancreatic duct injection (*n*)	23	17
Single pancreatic duct injection (*n*)	23	17
2–3 pancreatic duct injections (*n*)	11	15
> 3 pancreatic duct injections (*n*)	1	7
Difficult cannulation (*n*)	14	23

Post-procedure pancreatitis occurred in seven octreotide-treated patients (12.0%) and in eight controls (14.3%).

According to the Atlanta criteria, pancreatitis was mild in all cases.[28] Pancreatitis-related hospital stay was 3 days (mild pancreatitis) in four patients from the control group and five in the treatment group; between 4 and 10 days (moderate pancreatitis) in four controls and two patients in the treatment group.[22] No cases required more than 10 days in hospital and no local or systemic complications occurred.

No significant differences were detected between the two groups in the incidence or severity of pancreatitis. Length of hospital stay was not different in the two groups, although there were twice as many with a 4–10-day hospital stay in the control group.

At 24 h, hyperamylasemia was more than five times the upper normal limit, without pain, in three octreotide-treated patients (5.2%) and six controls (10.7%). Although apparently striking, this difference was not significant. Forty-eight patients in the octreotide group (82.8%) and 42 in the control group (75.0%) had serum amylase lower than five times the upper normal limit and did not suffer from pancreatic-like pain; again, although more patients in the octreotide group could have been discharged 24 h after the procedure, the difference was not significant.

Ten patients (17.2%) in the octreotide group and 14 controls (25.0%) had 24-h amylasemia more than five times the upper normal limit (a condition that required one additional day in hospital in our study), or suffered from post-procedure pancreatitis.

At 4–6 h, pancreatic-like pain was reported by 15 patients in the octreotide group (25.9%) and 16 in the control group (28.6%), irrespective of the serum amylase value. Amylasemia more than five times the upper normal limit without pain, and pain with serum amylases less than five times the upper normal limit occurred in one treated case and three controls.

Twelve patients (20.7%) in the octreotide group and 13 controls (23.2%) suffered from post-procedure pancreatic-like pain and had amylasemia more than five times the upper normal limit. Overall, 4–6 h after the endoscopic procedure, 16 patients (27.6%) in the octreotide group and 17 (30.4%) in the control group could not have been discharged.

Table 3. Numbers and percentages of patients with either serum amylase more than five times the upper normal limit, or pancreatic-like pain, or both, 2 h, 4–6 h and 24 h after the endoscopic procedure

		2 h after the endoscopic procedure				4–6 h after the endoscopic procedure				24 h after the endoscopic procedure			
		Octreotide		Control		Octreotide		Control		Octreotide		Control	
Serum amylase	Pancreatic-like pain	*n* cases	%	*n* cases	%	*n* cases	%	*n* cases	%	*n* cases	%	*n* cases	%
Less than five times the upper normal limit	Absent	44	75.9	39	69.6	42	72.4	39	69.6	48	82.8	42	75.0
	Present	5	8.6	5	8.9	3	5.2	3	5.4	—	—	—	—
More than five times the upper normal limit	Absent	1	1.7	1	1.8	1	1.7	1	1.8	3	5.2	6	10.7
	Present	8	13.8	11	19.6	12	20.7	13	23.2	7	12.0	8	14.3

DISCUSSION

The ideal pharmacological prevention of pancreatitis after ERCP should be effective in patients who really risk developing post-procedure pancreatitis; it should not require prolonged administration in the post-procedure period, and should be as cheap as possible. The mean incidence of post-procedure pancreatitis probably depends on the percentage of patients or procedures with some risk factors. Although the mean incidence of post-ERCP pancreatitis has been reported to range in non-selected patients from 1.3% to 5.2%, in the four prospective studies giving separate figures for standard- and high-risk patients, the reported incidence of pancreatitis was 1.6% and 7.8%, 3.4% and 29.2%, 3.6% and 19.1%, and 0.4% and 18.8%, in patients without and with sphincter of Oddi dysfunction, respectively.[1–3, 5, 8, 9]

With an incidence of 5% or less in non-selected patients, a prophylactic approach does not seem useful in most cases and is therefore costly if used in all cases; on the other hand, with the higher incidence in patients with risk factors (8–29%), a prophylactic approach may not only be justified, but would also be cost-effective.

Protease inhibitors reduce post-procedural hyperamylasemia and pancreatitis, but at substantial additional overall cost.[6, 29, 30] A theoretical analysis of cost-effectiveness and cost–benefit ratios of gabexate mesilate in post-ERCP pancreatitis confirmed that with an average 2% post-procedure pancreatitis rate, as reported for non-selected patients in recent studies, and an estimated 50% efficacy of the drug, routine prophylaxis appears too expensive.[31]

Somatostatin has proved effective in most studies, but it also needs continuous 12-h intravenous infusion, is expensive and requires an overnight hospital stay.[13]

The efficacy of octreotide has been evaluated in several trials with different therapeutic regimens. The simplest and cheapest prevention strategy, with a 100-μg subcutaneous bolus immediately before and 1 h after ERCP and sphincterotomy, did not lower the incidence of post-ERCP hyperamylasemia or modify the risk of pancreatitis.[15–17] This prophylactic approach did ensure a peak serum level at the time of papillary manipulation, and a subsequent subcutaneous dose was given to obtain a longer post-procedure effect. Therefore, the aim of this study was to inhibit exocrine pancreatic secretion within the first hour after papillary manipulation. Failure of this approach may be due to the excitatory effect of octreotide on the sphincter of Oddi, which raises the basal pressure and the frequency of phasic contractions, thus making papillary cannulation difficult and possibly even increasing the risk of post-procedural pancreatitis.[7, 15, 32, 33] It has also been suggested that the dosage used has no effect on the enzyme secretion.[34]

Experimental and clinical evidence that prolonged the administration of the peptide and lowered the levels of the enzymes in the pancreas led us to investigate the prophylactic effect of 3×200 μg/day of octreotide, starting 24 h before the endoscopic procedure, for the prevention of post-ERCP pancreatitis in subjects with patient-related risk factors for this complication.[35, 36]

The rationale for the trial was: (i) administration of the cheapest drug available known to profoundly inhibit exocrine pancreatic secretion; (ii) marked reduction of enzyme content in the pancreas at the time of ERCP, obtained by strong, prolonged reduction of amino acid uptake by pancreatic acinar cells; (iii) 24-h prophylaxis, that could be started the day before the procedure, either in hospital, without requiring additional time once the procedure is decided, or at home by the patients themselves if hospital admission is scheduled for the same day as the procedure; (iv) no excitatory effects on the sphincter of Oddi, because the peptide is not given immediately before the procedure, but at least 1 h before (the peak serum level of subcutaneous octreotide is reached within 30 min, with a half-life of about 113 min); (v) no prolonged medication required after the procedure, so prophylaxis is possible for patients scheduled for discharge the same day; (vi) prophylaxis only given to subjects with patient-related risk factors, who probably have the highest risk of developing post-procedure pancreatitis.

We decided not to use a placebo arm, because the significant efficacy of long-term subcutaneous octreotide on the post-procedure serum amylase curve and pain had already been documented in a blind, placebo-controlled trial.[18] Pancreatitis was defined according to objective parameters and predefined factors affecting the length of hospital stay were adopted in order to avoid bias. The equal distribution of patients in the treated and control groups in each centre, and the similar expertise in ERCP procedures, avoided bias due to the case-mix.

Pancreatitis occurred in 12.0% and 14.3% in the treated and control groups; this is similar to the rates reported in the literature for high-risk patients. No cases of severe pancreatitis were reported; octreotide did not

affect the incidence of mild pancreatitis (hospital stay for 3 days or less), but cases of moderate pancreatitis (4–10 days in hospital) were halved in the treatment group.

Twenty-four hours after the procedure, amylasemia more than five times the upper normal limit, without pain, requiring 1 more day in hospital for further monitoring, occurred about twice as often in the control group (10.7%) as in the octreotide group (5.2%); the difference, although striking, was not statistically significant. Overall, 24 h after the procedure, 82.8% of the octreotide group and 75.0% of the control group could be discharged from hospital.

Octreotide prophylaxis did not change the rate of possible same-day discharge. Between 4 and 6 h after the procedure, 72.4% of patients in the octreotide group and 69.6% of controls could be discharged, being asymptomatic, with serum amylase less than five times the upper normal limit.

In contrast with other studies in which octreotide was administered immediately before the endoscopic procedure, difficult cannulation of either Vater's papilla or of the desired duct (mainly the common bile duct) was reported more in the control group. This confirms that subcutaneous injection of the drug at least 1 h before the procedure does not affect sphincter of Oddi motor function, as we previously reported.[18] However, the post-procedure pancreatitis rate did not differ in the two groups, although it should theoretically have been higher in the control group, where there were more cases with both difficult cannulation and several pancreatic duct injections. This figure might be taken to indicate a lack of protective effect of octreotide. On the other hand, the male:female ratio was 1:2 in the octreotide and approximately 1:1 in the control group. The study design did not include female sex as a risk factor for post-ERCP pancreatitis, although a previous study did.[5] However, the higher prevalence of female sex in the octreotide group might have played in favour of some protective effect in high-risk subjects.

Overall, these conflicting data did not provide further evidence of a difference between treated and untreated patients.

This study is the first addressing the question of pharmacological prophylaxis for post-ERCP pancreatitis in patients known to have some high-risk condition for this complication. Octreotide, the only drug that can be used for prophylaxis in an out-patient setting, and with the lowest cost, proved ineffective at the dosage used. However, it was of some advantage in reducing the severity of post-procedure pancreatitis and the length of hospital stay. It may be worth testing octreotide at different dosages or in larger series of high-risk subjects or assessing the efficacy of somatostatin and gabexate mesilate, possibly reducing the length of intravenous administration of the latter drugs, in order to permit prophylaxis in an out-patient setting.

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