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A RANDOMIZED, DOUBLE-BLIND TRIAL OF THE EFFICACY OF OCTREOTIDE ACETATE ADMINISTRATION IN THE PREVENTION OF ABDOMINAL PAIN FOLLOWING THERAPEUTIC ENDOSCOPIC RETROGRADE CHOLANGIOPANCREATOGRAPHY

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SUMMARY – Abdominal pain is a complication of endoscopic retrograde cholangiopancreatography (ERCP) and endoscopic sphincterotomy (EST). The aim of this trial was to investigate the effects of octreotide acetate in the prevention of abdominal pain in patients undergoing therapeutic ERCP. A double-blind study was carried out in 209 subjects who were randomly allocated to two groups (A and B). Group A (104 patients) received 0.5 mg of octreotide acetate subcutaneously one hour prior to ERCP; and group B (105 patients) were given placebo. Patients were assessed 2 and 24 hours following endoscopy for the following parameters: presence and character of abdominal pain, requirements of analgetics. Thirty-nine (18%) patients complained of post-ERCP pain, i.e. ten in group A and 29 in group B, all of them treated with analgetics. Of the ten group A patients, symptoms of acute pancreatitis were identified in four (3.85%) patients *versus* ten (9.52%) patients in the control group B. The results obtained in the study seem to indicate that octreotide pretreatment significantly reduced the development of post-ERCP pain.

Key words: *Cholangiopancreatograopy, endoscopic, retrograde, adverse effects; Octreotide, therapeutic use; Pancreatitis, prevention and control*

Introduction

Complications related to endoscopic retrograde cholangiopancreatography (ERCP) represent a serious medical problem for both the patient and physician. Possible complications following this procedure include a rise in serum amylase and lipase, acute pancreatitis, and epigastric pain[1]. The incidence of pancreatitis as the most severe complication following ERCP has been variously assessed to lie between 2% and 20%[1]. However, the frequency of biochemical abnormalities (increased serum pancreatic enzyme values) without clinical manifestations of acute pancreatitis is much higher, i.e. as much as 75% of patients according to a review by Booth et al.[2], while episodes of post-ERCP epigastric pain have not been fully investigated.

The pathogenesis of post-ERCP pain is not known. Some cases might have previously been explained by forced filling of the pancreatic duct and use of ionic contrast medium[3]. However, avoiding 'acinarization' in pancreatogram and changing to nonionic contrast medium have not made post-ERCP pancreatitis disappear. Likewise, the presence of abdominal pain, with or without serum pancreatic enzyme increment, remains another scenario that may be expected following ERCP[4].

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Few drugs have been used in the prevention of post-ERCP complications, among which octreotide, a somatostatin analogue (Sandostatin, Sandoz) has been assessed due to its unique pharmacologic properties[5-7]. Several studies in healthy volunteers have shown inhibition of baseline and stimulated exocrine pancreatic secretion[7-9]. Likewise, animal studies have shown an impairment in the pancreatic enzyme response after an infusion of octreotide[10]. In one study, pancreatitis was induced by ligature of the pancreatic duct[11], a model that is probably more analogous to post-ERCP pancreatitis. Octreotide improved the enzyme response, histology, and survival.

Several studies have dealt with evaluating the prophylactic effects of octreotide on ERCP-induced pancreatic reactions, but the results of such studies have been conflicting and few authors have dealt specifically with the problem of post-ERCP epigastric pain[12-16]. Our group had previously investigated the single-dose prophylactic effects of octreotide in preventing the increase in serum pancreatic enzymes in a group of hospitalized patients undergoing therapeutic ERCP[17]. The focus of this paper will be to detail the effects of prophylactic octreotide administration on abdominal pain, observed in the previously mentioned population, i.e. in the patients who received a single dose of octreotide acetate prior to ERCP.

Patients and Methods

During a four-year period (September 1994 – September 1998), a total of 209 subjects with indications for therapeutic ERCP were enrolled in the trial designed as a randomized, double-blind study. Randomization was performed using the Microsoft Excel software. Subjects were allocated to either of two groups (A and B), and underwent prophylactic treatment with either octreotide acetate or placebo (Table 1). Blinding was ensured by the study solutions being prepared by the same individual not present during the procedure but given the list of randomization. Patients allocated to group A were administered 0.5 mg of octreotide subcutaneously one hour prior to the endoscopic procedure. Patients from group B (placebo group) were administered isotonic sodium chloride in the protocolar fashion. Prior to the procedure (which was always performed by the same endoscopist), all patients underwent the same premedication which consisted of sublingual administration of nitroglycerin, intravenous administration of 10 mg diazepam, and pharyngeal anesthesia with Xylocaine spray. Likewise, all patients received antibiotic prophylaxis in the form of ciprofloxacin 90 minutes before ERCP. All patients were hospitalized and confined to bed for at least 24 hours following ERCP. Fasting was maintained for a minimum of six hours.

Assessment of abdominal pain was performed prior to ERCP, and 2 and 24 hours after ERCP. Pain was graded using a simple scoring system in which patients categorized their pain into one of 4 categories assigned values from 0 to 4, as follows: 0 – no pain, 1 – mild pain, 2 – moderate pain, and 3 – severe pain. Patients who complained of pain were asked about its location and character, whether it was similar to the pre-existing pain, and whether there was radiation to the back. For those patients who required pain medication, the type of medication, route of administration and dose were recorded.

ERCP was performed using an Olympus JF1T20 endoscope. Contrast medium (Urografin, Schering AG Pharma, Germany) was injected manually in a controlled, titrated fashion under fluoroscopic control. When indicated, sphincterotomy was performed using a standard Erlangen type sphincterotomy. Selective cannulation was performed in all patients. Ductal cannulation was rated as 'easy' if cannulation could be readily achieved, or 'difficult' if it required repeated attempts.

ERCP pancreatitis was defined as the presence of abdominal pain, tenderness, nausea and vomiting beginning after ERCP and lasting for at least 24 hours, associated with an increase in serum amylase and/or lipase levels greater than three-fold upper 'normal' limit. It was graded as mild if admission or prolongation of the planned admission by 1 to 3 days was required; moderate for hospitalization not longer than 10 days; and severe for any intensive care unit admission, hospital stay of more than 10 days, hemorrhagic pancreatitis, phlegmon, or pseudocyst formation.

Comparison of data between the two groups was done by use of Cochran-Mantel-Haenszel analysis. A p value of 0.05 or less was considered as indicating statistical significance.

The study was approved by the Hosptial Ethics Committee. Prior to enrollment in the study, all patients were informed about the nature of the study, and a written informed consent was obtained.

Results

Of 209 patients enrolled in the study, 104 were treated with octreotide, while 105 patients were given placebo and

served as a control group (Table 1). The mean duration of endoscopic procedure in the octreotide and control group was 34 and 31 minutes, respectively, with an average of 15 ml of contrast medium used in all patients. No significant side effects attributable to octreotide were observed during the study.

Table 1. Patient characteristics

Patients	Group A (octreotide acetate)	Group B (control group; placebo)
n	104	105
Mean age (yrs)	56	54
Sex (M/F)	40/64	45/60

Thirty-nine patients complained of pain following therapeutic endoscopic procedure, i.e. ten group A patients and 29 group B patients, all of them treated with analgesics (Table 2). Out of the ten group A patients, symptoms of acute pancreatitis were identified in four (3.85%) patients *versus* ten (9.52%) in the control group. The patients who developed acute pancreatitis were included in the highest score group.

Table 2. Abdominal pain score according to patient group

Pain score	Group A (octreotide acetate) (n = 104) n (%)	Group B (control group; placebo) (n = 105) n (%)
0	94 (90.3)	76 (73)
1	5 (4.8)	2 (1.9)
2	1 (1.0)	10 (9.5)
3	4 (3.8)	17 (16.2)
Level of significance	p<0.01*	

* statistically significant different between-group pain score distribution

Apart from the patients who developed acute pancreatitis and were treated conventionally, the patients with mild and moderate pain (score 1 or 2) were treated with i.v. metamisol (Analgin, Pliva, Zagreb, Croatia), while those with a pain score 3 and without symptoms of acute pancreatitis were treated with s.c. pentazocine (Fortral, Krka, Novo Mesto, Slovenia).

Discussion

Complications related to ERCP pose a serious medical problem for both the patient and the physician. One of the procedure complications is the development of post-ERCP epigastric pain. Since somatostatin has been demonstrated to relieve post-ERCP epigastric pain[18], it seemed reasonable to presume that octreotide, a potent somatostatin analogue, might elicit a similar effect. In the present study, we tried to determine whether octreotide acetate prophylaxis could decrease the incidence of epigastric pain in patients undergoing therapeutic ERCP. We hoped to help clarify the issue by comparing the reported presence and severity of pain in the group of patients administered a single dose of octreotide s.c. one hour before the endoscopic procedure (group A) and in the group of patients who received isotonic sodium chloride by the same route of administration. Our choice of a single dose instead of longterm octreotide administration, described by Testoni et al.[16], was based on the fact that in spite of the octreotide half-life of 90-120 minutes with s.c. administration, its pharmacodynamic action lasts for up to 8-12 hours[8], i.e. for a period of time when the post-ERCP complications develop.

Post-ERCP epigastric pain with or without the development of pancreatitis is commonly observed, however, the cause of its occurrence has not yet been fully clarified. One explanation could be the reduced pancreatic secretion against the temporarily obstructred sphincter of Oddicaused by both instrumental manipulation and forced filling of the pancreatic duct 5,19,20. It has recently been demonstrated that octreotide acetate, among its other pharmacologic actions, restrains the Oddi's sphincter motility 21. This type of drug action should reduce pressure in the intrapancreatic ducts, thus helping prevent the occurrence of acute pancreatitis.

Our study in 209 patients randomized to octreotide or placebo administration showed a significant effect of octreotide in preventing the development of post-ERCP abdominal pain (Table 2). Thirty-nine patients complained of post-ERCP pain, i.e. ten patients on octreotide and 29 patients from the control group receiving placebo (p<0.05), all of them treated with analgesics. Out of the ten octreotide group patients, symptoms of acute pancreatitis were recorded in four patients, as compared with ten

out of 29 control group patients. In the patients administered octreotide who developed abdominal pain, there was a tendency to mild (five octreotide group patients *versus* two control group patients) rather than moderate pain (one octreotide group patient *versus* ten control group patients), with lower use of analgesics. In the octreotide group, severe pain was only recorded in patients who were classified as having developed acute pancreatitis, while in the placebo group severe pain was reported by seven patients otherwise free from other indicators of acute pancreatitis (tenderness, nausea and vomiting beginning after ERCP and lasting for at least 24 hours, associated with an increase in serum amylase and/or lipase levels greater than three-fold upper normal limits).

In conclusion, the results obtained in the present study seem to indicate that a single application of octreotide can prevent the development of abdominal pain after ERCP, with a tendency to mild pain when it does occur, and with a lower use of analgesics. Therefore, it appears that octreotide prophylaxis might have an important role in therapeutic ERCP procedures.

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Sažetak

RANDOMIZIRANO DVOSTRUKO-SLIJEPO ISPITIVANJE UČINKOVITOSTI OKTREOTID ACETATA U SPRJEČAVANJU ABDOMINALNE BOLI NAKON TERAPIJSKE ENDOSKOPSKE RETROGRADNE KOLANGIOPANKREATOGRAFIJE

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Abdominalna bol je česta komplikacija endoskopske retrogradne kolangiopankreatografije (ERCP) i endoskopske sfinkterotomije (EST). Cilj ovoga ispitivanja bio je istražiti učinke oktreotid acetata u prevenciji abdominalne boli u bolesnika podvrgnutih ERCP-u. U ovu dvostruko-slijepu studiju bilo je uključeno 209 bolesnika koji su nasumce podijeljeni u dvije skupine (A i B). Bolesnici skupine A (n=104) primili su 0,5 mg oktreotid acetata supkutano jedan sat prije ERCP-a, dok su bolesnici skupine B (n=105) dobili placebo. Procjena kliničkih parametara (prisutnost i težina abdominalne boli te potreba za analgeticima) provedena je u bolesnika 2 i 24 sata nakon endoskopije. Ukupno se 39 (18%) bolesnika žalilo na bol nakon ERCP-a, tj. desetoro u skupini A i 29 u skupini B, a svi su oni liječeni analgeticima. Od desetoro bolesnika iz skupine A simptomi akutnog pankreatitisa zabilježeni su u četvoro (3,85%) bolesnika, u usporedbi s desetoro (9,52%) bolesnika u kontrolnoj skupini B. Rezultati ovoga ispitivanja pokazali su da je prethodno davanje oktreotida značajno smanjilo nastup abdominalne boli nakon ERCP-a.

Ključne riječi: *Kolangiopankreatografija, endoskopska, retrogradna, nuspojave; Oktreotid, terapijska primjena; Pankreatitis, prevencija i suzbijanje.*