POLSKI
PRZEGLĄD CHIRURGICZNY
2015, 87, 12, 620–625

10.1515/pjs-2016-0013

ASSESSMENT OF PHARMACOLOGICAL PROPHYLAXIS FOR ACUTE PANCREATITIS FOLLOWING ERCP IN PATIENTS WITH CHOLEDOHOLITHIASIS

EWA ŁUBOWSKA-PAJĄK[1], *KRZYSZTOF KOŁOMECKI*[2]

Department of General and Oncological Surgery, Kutno Local Government Hospital (Non-public Health Care Institution[1]
Kierownik: dr n. med. *Z. Adamczyk*
Department of General and Endocrine Surgery, Medical University in Łódź[2]
Kierownik: prof. dr hab. *K. Kuzdak*

Endoscopic retrograde cholangiopancreatography (ERCP) is an effective tool in the diagnostics and treatment of bile duct diseases. Although minimally invasive, the procedure is associated with a risk of complications, with acute pancreatitis being the most serious. In recent years, high hopes have been placed on pharmacological prevention of acute pancreatitis after ERCP.

The aim of the study was assessment of the efficacy of low-molecular-weight heparin and somatostatin in combination with diclofenac in the prevention of acute pancreatitis after ERCP.

Material and methods. The study enrolled three groups of 30 patients diagnosed with cholelithiasis; group I: patients who received low-molecular-weight heparin prior to ERCP, group II: patients who received somatostatin and diclofenac, group III: control group. The study assessed the incidence of acute pancreatitis, hyperamylasemia and increased CRP levels.

Results. Acute pancreatitis was observed in 13.3% of group I patients, 10% of group II patients and 16.7% of group III patients (no statistical significance). Hyperamylasemia was observed in 16.7% of group I patients, 16.7% of group II patients and 43.3% of group III patients. These differences were statistically significant. No significant differences were found in the occurrence of increased CRP levels among the study groups.

Conclusions. No significant reduction in the occurrence of acute pancreatitis after ERCP was observed in patients who received pharmacological prophylaxis. A significant reduction in the occurrence of hyperamylasemia was found in drug-treated patients.

Key words: acute pancreatitis, endoscopic retrograde cholangiopancreatography

Minimally invasive surgical procedures have developed immensely during the last 10+ years. Endoscopic retrograde cholangiopancreatography (ERCP) is one of the leading examples and has been performed since 1968 (1). This date marks a change in the scope of interventions performed during this procedure. During ERCP, it is not only possible to incise the hepatopancreatic ampulla and remove deposits from the bile duct and break up larger deposits, but also to insert a prosthesis to widen the place of stenosis, allowing the unconstrained flow of bile as well as the collection of brush swab samples and specimens for histopathological examination.

The most common indication for ERCP is mechanical jaundice in the course of choledocholithiasis. Other indications include: biliary pancreatitis, pancreatic tumours, hepatopancreatic and bile duct ampullae. Most patients may simultaneously undergo a medical procedure to restore the unconstrained flow of bile.

Choledocholithiasis is observed in 8.2% of men and nearly 18% of women in the Polish urban population. The condition is twice more common in women (2). Attempts at removing deposits should always be preceded by the inci-

sion of the hepatopancreatic ampulla sphincter. Ampulla dilatation with a balloon was proposed in the 1980s as an alternative to sphincterotomy. When performed alone, the procedure was associated with a greater risk of acute pancreatitis. However, ampulla dilatation with a large balloon following sphincterotomy was found to be safer and more effective, especially in the case of large-diameter deposits (3).

Although ERCP is considered minimally invasive, the procedure is associated with a risk of complications. Acute pancreatitis is the most common complication with an incidence of 1-30% (4). Haemorrhage, perforation and cholangitis are less common. Therefore, great emphasis has been placed in recent years on the prevention of acute pancreatitis after ERCP, from the appropriate selection of patients qualified for ERCP, the choice of procedure, the use of prostheses, to pharmacological prevention. Attempts at the pharmacological prevention of acute pancreatitis after ERCP were first made in 1978. A number of drugs with the potential to prevent acute pancreatitis after ERCP were studied. The drugs that have been analysed to date include somatostatin, heparin, ocreotide, allopurinol, interleukin-10, gabexate, antibiotics, botulinum toxin, steroids, nitroglycerin, diclofenac, lignocaine, nifedipine, N-acetylcysteine, ulinastatin and epinephrine.

Heparin is produced by the body's mast cells (e.g. in the liver, heart, lungs and intestines) and exhibits anticoagulant activity. Heparin also displays anti-inflammatory, antiviral, immunosuppressive, antipsoriatic and hypolipidemic (cholesterol-lowering) activity.

The inflammatory and coagulation processes are closely linked. Inflammatory cytokines activate coagulation due to increased tissue factor expression on monocytes and the vascular endothelium, leading to the production of thrombin and fibrin. On the other hand, the activation of coagulation stimulates inflammatory processes.

The mechanism of the anti-inflammatory activity of heparin is complex and has not been fully understood. The anti-inflammatory activity of heparin was first observed in the 1960s when the administration of intravenous and later nebulised heparin was shown to reduce symptoms of bronchial asthma. In the 1990s, a mild beneficial effect of heparin on the clinical course and healing process in ulcerative colitis and skin and respiratory tract burns was found (12 -15).

Somatostatin was isolated in 1973; this hormone is not secreted by one particular gland. Apart from the hypothalamus, somatostatin has been shown to be released by the central nervous system, thyroid and placenta, and to be present in the D cells of the gastrointestinal mucosa and pancreas. Somatostatin inhibits the secretion of gastric acid, pancreatic juice, bile, and peristalsis. It reduces the concentration of other tissue hormones and acts oppositely to secretin. Somatostatin is used in the treatment of acute gastrointestinal haemorrhage, intestinal and pancreatic fistulae, in the symptomatic treatment of excessive secretion from gastrointestinal endocrine tumours, and in the prevention of complications after surgery. Somatostatin was shown to reduce the concentration of gastrin in healthy individuals, in patients with pernicious anemia and patients with Zollinger–Ellison syndrome. Somatostatin was recently shown to inhibit the secretion of the vasoactive intestinal peptide (VIP) in patients with Verner-Morrison syndrome.

Diclofenac is a first generation NSAID with potent anti-inflammatory and analgesic activity. It is quickly and completely absorbed from the gastrointestinal tract. Maximum plasma concentrations are achieved within 1–2 hrs, and in the synovial fluid, 2–4 hrs. Plasma concentrations remain in a linear dose-response relationship. Half-life in blood and synovial fluid is 2 hrs. Diclofenac inhibits platelet aggregation (albeit less and shorter than acetylsalicylic acid).

The aim of the study was assessment of the efficacy of low-molecular-weight heparin and somatostatin in combination with diclofenac in the prevention of acute pancreatitis after ERCP.

MATERIAL AND METHODS

The study was prospective.

The study enrolled patients:

– diagnosed with cholelithiasis according to imaging tests (abdominal ultrasound, abdominal CT scan, abdominal MRI scan),
– aged 25-65,
– previously non-hospitalised for acute pancreatitis,

– who underwent ERCP for the first time.

The following patients were excluded form the study: patients with a diagnosis of pancreatitis confirmed by laboratory tests performed prior to ERCP, patients after bile duct or duodenum surgery, patients diagnosed with bile duct, hepatic, duodenal, gastric, small intestine or colon cancer.

Participants were randomised to three groups of 30 people:

– group I received low-molecular-weight heparin prior to ERCP,

– group II received a single intravenous dose of somatostatin 12 hours prior to the procedure and a diclofenac suppository immediately before ERCP,

– group III was the comparison group.

Heparin was injected subcutaneously in the form of Fraxiparine at a dose of 0.3 ml, 12 hours prior to the procedure. Somatostatin at a dose of 250 micrograms was administered intravenously 12 hours prior to the procedure, while diclofenac was administered rectally at a dose of 150 milligrams before the procedure.

The study assessed the incidence of acute pancreatitis, hyperamylasemia, hyperamylasemia with increased blood serum CRP levels and increased CRP alone without any other inflammation markers.

Acute pancreatitis was diagnosed based on:

1) clinical symptoms: acute onset epigastric pain, often radiating to the back, nausea, vomiting, fever;
2) b lood serum lipase or amylase levels >3-fold above the upper limit of normal. The normal blood serum level was adopted at 0-60 U/L for lipase and 28-100 U/L for amylase.

Hyperamylasemia and hyperlipidemia were defined as a 2-fold increase in serum lipase or amylase levels, i.e. 120-180 U/L for amylase and 200-300 U/L for lipase. Further in this paper I will only use the term "hyperamylasemia".

The adopted cut-off point for CRP was above 100 mg/l.

17 women and 13 men qualified to the group that received Fraxiparine preventively. Of those, 16 had their deposits removed, 9 had a prosthesis inserted in the common bile duct in addition to deposit removal, and no deposits were found in the bile duct of 5 patients. 19 women and 11 men qualified to the group that received somatostatin with diclofenac. Deposits were removed in 14 of these patients, deposits were removed and common bile duct prostheses inserted in 10, and a revision of the bile duct was performed in the remaining patients.

21 women and 9 men qualified to the control group. Deposits were removed in 19 patients, and in 5 patients, deposits were removed and a prosthesis was inserted in the common bile duct. A revision of the bile duct was performed in 6 patients and no deposits were found.

RESULTS

In group I, a 3-fold increase in blood serum lipase or amylase levels was observed in 4 patients. High CRP levels were found in each of these patients. High pancreatic inflammation markers correlated with pain in the left epigastric region. Among the remaining patients, a 2-fold increase in blood serum amylase or lipase levels was observed in 5 patients. Each of these patients had elevated CRP. Additionally, an increase in CRP above 100 mg/l with no other pancreatic inflammation markers was observed in 3 patients. The hospitalisation period was not prolonged in these patients.

In group II, acute pancreatitis was diagnosed in 3 patients. 5 patients were diagnosed with hyperamylasemia. Hyperamylasemia was observed concomitantly with high CRP levels in 4 patients. Moreover, 1 patient had increased blood serum CRP levels without any other inflammation markers. These results did not extend the hospitalisation period in any of these patients.

In group III, a 3-fold increase in blood serum lipase levels was observed in 5 patients. Similarly to the previous group, these patients experienced pain in the epigastric region and had elevated CRP. Transient hyperamylasemia was observed in 13 patients. In 9 patients this was associated with elevated CRP. No case of spontaneous CRP elevation above 100 mg/l without elevated pancreatic enzymes was observed.

One control group patient was diagnosed with necrotising pancreatitis which led to multiple organ failure and death. In this patient, an over 3-fold increase in amylase levels

Table 1. Group composition by age

	Group I	Group II	Group III
Women	17 (56,7%)	19 (63,3%)	21 (70%)
Men	13 (43,3%)	11 (36,7%)	9 (30%)

Table 2. Procedures performed during ERCP

	Group I	Group II	Group III
Removal of deposits	16 (53,3%)	14 (46,7%)	19 (63,3%)
Removal of deposits + bile duct prosthesis	9 (30%)	10 (33,3%)	5 (16,7%)
Bile duct revision	5 (16,7%)	6 (20%)	6 (20%)

Table 3. The incidence of complications after ERCP by group

	Group I	Group II	Group III	p
Acute pancreatitis	4 (13,3%)	3 (10%)	5 (16,7%)	0,749
Hyperamylasemia	5 (16,7%)	5 (16,7%)	13 (43,3%)	0,024
Hyperamylasemia with high CRP	5 (16,7%)	4 (13,3%)	9 (30%)	0,233
Elevated CRP without pancreatic inflammation markers	3 (10%)	1 (3,3%)	0 (0%)	0,127

p – probability of random distribution; comparison of groups using the chi-square test

was observed within 24 hours after ERCP. This correlated with an increase in CRP above 100 mg/l. Within 2 hours of the procedure, the patient reported pain which escalated significantly over the subsequent 10+ hours. After 5 days, amylase levels decreased and exceeded normal levels 2-fold. The pain disappeared. CRP levels remained unchanged until the patient's death on day 13.

The incidence of acute pancreatitis in groups that received medications did not differ significantly from the control group. The hospitalisation period of these patients was extended by 4-8 days. The course of the disease was mild in most patients, patients responded well to conservative treatment and none required the use of antibiotics. One control group patient died on day 13 after ERCP. She had developed pancreatic necrosis with a severe course. Despite parenteral feeding and antibiotic therapy, the patient developed multi organ failure which resulted in death. Hyperamylasemia was observed significantly less common in patients who received low-molecular-weight heparin and somatostatin with diclofenac compared with the placebo group. The clinical course was mild in these patients. The hospitalisation period was extended by 2-4 days in 3 group III patients. The incidence of pancreatic reaction with high CRP levels was not statistically different among the groups. 2 control group patients and 2 patients who received Fraxiparine were hospitalised 2-3 days longer.

Elevated CRP levels (above 100 mg/l) alone were observed in 3 group I patients and 1 group II patient. This was not associated with additional complications.

DISCUSSION

Acute pancreatitis is the most common complication after ERCP. Depending on the centre, the condition affects 1.3%-30% of patients. According to Cotton's criteria (adopted in 1991), acute pancreatitis after ERCP is diagnosed in patients who experience abdominal pain after the procedure with a concomitant ≥3-fold increase in blood serum amylase activity

that persists 24 hours after ERCP, and who require hospitalisation (5). Transient hyperamylasemia occurs in up to 70-75% of patients and amylase levels normalise within 24 hours after ERCP (6, 7).

The risk factors for acute pancreatitis after ERCP may be either patient-related or associated with the procedure. According to Cheng, patient-related factors include young age, fe-

male sex, sphincter of Oddi dysfunction, a history of acute pancreatitis after ERCP, the presence of anatomical variants of the pancreas, and normal serum bilirubin levels.

Factors associated with the procedure include the need for sphincterotomy, the number of attempts at cannulation, the injection of contrast material into the bile ducts, and manipulation of the biliary tract. All patients eligible for the procedure were aged 25-65 and were mostly female: women constituted 63.33% of all patients who underwent the procedure.

In 2007, Andrulli et al. published the results of 21 studies from 1997-2006 that dealt with complications after ERCP and encompassed 16855 patients. The author concluded that complications after ERCP were observed in 6.85% of patients and death, in 0.33%. The most commonly reported complications included acute pancreatitis (3.47%), bacterial infections (1.44%), haemorrhage (1.34%) and periampullary perforation (0.60%) (8).

In 2002, Rabenstein et al. presented study results showing the incidence of acute pancreatitis after ERCP in comparison with patients who received preventive heparin treatment. The control group was made up of 547 patients and 268 patients received heparin prior to ERCP. The incidence of acute pancreatitis was lower in the heparin group compared with the control group: 3.4% vs 7.9%, respectively (9).

A group of Chinese authors performed a review and meta-analysis of studies on the potential benefits of administering low doses of heparin in the prevention of acute pancreatitis after ERCP. Li et al. analysed 7 studies that encompassed a total of 1438 patients. The authors did not observe a significant correlation between the use of heparin and a reduced incidence of acute pancreatitis after ERCP (10). On the other hand, Ung et al. published the result of his study which enrolled 89 patients. Half of these were given heparin before and after ERCP. Ung observed no significant increase in blood serum amylase, AspAT and ALAT in the heparin group, contrary to the control group (11).

In the presented study acute pancreatitis after ERCP was observed in 5 control group patients and 4 patients who received low-molecular-weight heparin (16.67% vs 13.33%). The percentage of patients with acute pancreatitis after ERCP was significantly higher than in studies by Andrulli et al. and Rabenstein et al. No correlation was observed between a lower risk of acute pancreatitis after ERCP in patients who received heparin as a preventive measure compared with the control group.

It is believed that somatostatin may have a beneficial effect on the prevention of acute pancreatitis after ERCP. However, the short half-life of this substance is problematic. Katsinelos et al. performed a study with 540 patients who were divided into 2 groups. The first group received somatostatin intravenously plus a diclofenac suppository, the second group received only a placebo suppository. The incidence of acute pancreatitis was 4.7% in the first group and 10.4% in the second group (16).

In our observations, the percentage of patients with acute pancreatitis after ERCP who received somatostatin and diclofenac was higher than in this study. A slight downward trend was shown in terms of disease incidence following the use of medications that did not bear statistical significance ($p<0.05$). In accordance with the study results shown here, I observed 1 death in the placebo group which constituted 3.3% of this group and 1.1% of all patients. This result is higher than worldwide data. This may likely be due to the low number of patients enrolled in the study. An appropriate patient qualification procedure for ERCP seems to be crucial. In light of the current advances in diagnostic imaging, the performance of ERCP in dubious indications is inadvisable. To date, no medicinal substance has been implemented as a routine preventive measure for acute pancreatitis after ERCP. The lack of an effective medicinal substance calls for further research. Further multicentre studies that enroll more patients are needed.

CONCLUSIONS

1. The use of low-molecular-weight heparin and somatostatin in combination with diclofenac prior to ERCP was not associated with a reduced incidence of acute pancreatitis.
2. Pharmacological prophylaxis prior to ERCP resulted in a significantly reduced incidence of pancreatic reaction in the form of hyperamylasemia.

REFERENCES

1. *Baillie J:* Training in advanced pancreaticobiliary endoscopy: why, how, and will we even need ERCP in the future? *Tech Gastrointest Endosc* 2004; 6:100-06.
2. *Attili AF, Capocaccie R, Carruli N* et al.: Factors associated with gallstone disease in the MICOL experience. Multicenter Italian Study on Epidemiology of Cholelithiasis. *Hepatology* 1997; 26 (4): 809-18.
3. *Attam R, Freeman ML:* Endoscopic papillary large balloon dilation for large common bile duct Stones. *J Hepatobiliary Pancreat Surg* 2009; 16: 618-23.
4. *Piotrowska-Staworko G, Świdnicka-Siergiejko A, BaniukiewiczA, Dąbrowski A:* Powikłania po endoskopowej cholangiopankreatografii wstecznej. *Gastroenterol Pol* 2007; 14 (4): 307-12.
5. *Cotton PB, Garrow DA, Gallagher J, Romagnuolo J:*. Risk factors for complication safter ERCP: a multivariate analysis of 11,497 procedures over 12 years. *Gastrointest Endosc* 2009 70 (1): 80-88.
6. *Testoni PA, Mariani A, Masci E* et al.: Frequency of post-ERCP pancreatitis in a single tertiary referral center without ant with routine prophylaxis with gabexate: a six-year survey. *Dig Liv Dis* 2006; 38: 588-95.
7. *Hellmig S, Fölsch UR:* Pharmacologicalprevention of post-ERCP pancreatitis – aneverlasting dream? *Dig Liver Dis* 2006 Aug; 38 (8): 588-95.
8. *Andriulli A, Loperfido S, Napolitano G* et al.: Incidencerates of post-ERCP complications: a systematic survey of prospective studies. *Am J Gastroenterol* 2007; 102: 1781-88.
9. *Rabenstein T, Roggenbuck S, Framke B* et al.: Complications of endoscopic sphincterotomy: can heparin prevent acute pancreatitis after ERCP? *Gastrointest Endosc* 2002 Apr; 55 (4): 476-83.
10. *Li S, Cao G, Chen X, Wu T:* Low-dose heparin in the prevention of post endoscopic retrograde cholangiopancreatography pancreatitis: a systematic review and meta-analysis. *Eur J Gastroenterol & Hepatol* 2012 May; 24 (5): 477-81.
11. *Ung KA, Rydberg L, Modin S* et al.: A preventive effect of unfractionated heparin on post-ERCP pancreatitis is suggested by positive effects on laboratory markers. *Hepatogastroenterol* 2011; 58: 168-73.
12. *Young E:* The anti-inflammatoryeffects of heparin and relatedcompounds. *Thromb Res* 2008; 122: 743-52.
13. *Mousa SA:* Heparin, low molecular weight heparin, and derivatives in thrombosis, angiogenesis, and inflammation: emerging links. *Semin Thromb Hemost* 2007; 33: 524-33.
14. *Walenga JM:* Non-anticoagulant effects of unfractionated and low-molecular weight heparins. Clin Adv Hematol Oncol 2007; 5: 759-60.
15. *Elsayed E, Becker RC:* The impact of heparin compounds on cellular inflammatory responses: a construct for future investigation and pharmaceutical development. *J Thromb Thrombolysis* 2003; 15: 11-18.
16. *Katsinelos P, Fasoulas K, Paroutoglou G* et al.: Combination of diclofenac plus somatostatin in the prevention of post-ERCP pancreatitis: a randomized, double-blind, placebo-controlledtrial. *Endoscopy* 2012; 44: 53-59.

Received: 29.12.2015 r.
Adress correspondence: 99-300 Kutno, ul. Kościuszki 52
e-mail: ewa_lubowska@o2.pl