Risk Factors for Post-Endoscopic Retrograde Cholangiopancreatography (ERCP) Pancreatitis and the Effect of Octreotide Combined with Nonsteroidal Anti-Inflammatory Drugs on Preventing Its Occurrence

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Background: The aim of this study was to explore the risk factors for post-endoscopic retrograde cholangiopancreatography (ERCP) pancreatitis and investigate the effect of octreotide combined with nonsteroidal anti-inflammatory drugs on preventing its occurrence.

Material/Methods: A total of 139 patients undergoing ERCP in our hospital from May 2016 to April 2017 were retrospectively analyzed, and divided into an observation group (n=67) (octreotide + indomethacin) and a control group (n=72) (no preventive drugs). The preoperative and postoperative inflammatory cytokines such as tumor necrosis factor-α (TNF-α), interleukin-6 (IL-6) and IL-8, and serum amylase levels were measured, and the incidence of pancreatitis and hyper amylasemia were monitored.

Results: Serum amylase level was increased significantly 3 hours after operation in both groups with significantly higher level in the control group compared to the observation group. After 24 hours, serum amylase in the observation group was decreased to preoperative level, whereas it was still higher than preoperative in the control group (P<0.05). Regarding the levels of TNF-α, IL-6, IL-8, and visual analogue scale, they were significantly increased in both groups after operation with significantly higher levels in the control group compared to the observation group (P<0.05). Furthermore, logistic regression analysis showed that difficult intubation, pancreatic duct angiography, surgery for a long time, and the history of previous pancreatitis were risk factors for post-ERCP pancreatitis (P<0.05).

Conclusions: Difficult intubation, pancreatic duct angiography, surgery for a long time, and the history of previous pancreatitis were risk factors for post-ERCP pancreatitis. Octreotide combined with non-steroidal anti-inflammatory drugs can reduce the pain of patients with abdominal pain as well as the incidence of postoperative pancreatitis, indicating that they might be effective preventative approaches for pancreatitis.

MeSH Keywords: Indomethacin • Octreotide • Pancreatitis

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Background

Endoscopic retrograde cholangiopancreatography (ERCP) is a technique which visualizes biliary and pancreatic ducts by x-ray photography through inserting a duodenoscope into the descending part of the duodenum to find the duodenal papilla, in which a radiographic catheter was inserted through the biopsy followed by injection of the contrast agents [1]. ERCP was first proposed and applied in the United States in the 1960s and can be used in the diagnosis of cholecystopancreatic diseases. In addition, ERCP is able to assist the performance of surgical procedures, with the advantages of small trauma and fast recovery, which is widely applied in the diagnosis and treatment of choledochal diseases in recent years [2]. As an invasive procedure, ERCP causes a series of complications such as hemorrhage, pancreatitis, infection, and high amylase (inevitably) after performance, resulting in more pain to patients [3]. Post-ERCP pancreatitis is manifested by abdominal pain, elevated amylase, etc., and during its onset, several inflammatory cytokines are released, leading to damage of distant organs and subsequent dysfunctions, which severely affects the post-ERCP rehabilitations of patients. If post-ERCP pancreatitis is not treated in time, it can easily develop into severe acute pancreatitis, or even death. Therefore, how to prevent the incidence of post-ERCP pancreatitis is very critical in clinic [4,5]. This study aimed to analyze the influencing factors of post-ERCP pancreatitis and investigate the effect of relevant drugs on the intervention of pre-ERCP intervention.

Material and Methods

Patients

The study protocol was approved by the Research Ethics Committee of our hospital. A total of 139 patients receiving ERCP in our hospital from May 2016 to April 2017 were recruited in this study. Inclusion criteria was: 1) patients who met ERCP indications [6]; 2) patients who or whose families signed the informed consent. Exclusion criteria was: 1) patients with coagulation disorders; 2) patients who were complicated with pancreatitis; 3) patients who were allergic to drugs used in this study; 4) pregnant or lactational women. The study patients were divided into the observation group (n=67, taking octreotide + indomethacin) and the control group (n=72, taking no preventive drugs) based on the receiving of preventive drug treatment. There were no significant differences in the basic characteristics of patients between the 2 groups (P>0.05) (Table 1).

Preventive treatment

Before ERCP, patients received routine examinations (blood routine examination, hepatic and renal function test, electrocardiographic examination, serum amylase examination, coagulation function test, etc.) to exclude patients with surgical contraindications, and were subjected to 8 hours of fasting. At 0.5 hours before ERCP, patients received conventional drugs intramuscularly to increase their surgical tolerance, including 10 mg scopolamine (manufacturer: Ningbo Dahongying Pharmaceutical Co., Ltd., approval number: NMPN H33020794), 50 mg pethidine (manufacturer: Shenyang No. 1 Pharmaceutical Plant of Northeast Pharmaceutical Group Co., Ltd., approval number: NMPN H21022413), and 10 mg diazepam (manufacturer: Tianjin Kingyork Pharmaceutical Co., Ltd., approval number: NMPN H12020957). In addition to the aforementioned drugs, patients in the observation group took octreotide (manufacturer: SPH No. 1 Biochemical and Pharmaceutical Co., Ltd., approval number: NMPN H20060176, usage and dosage: at 1 hour before ERCP, intravenous infusion of 0.3 mg for 24 hours), and indomethacin (manufacturer: Beijing Twinluck Pharmaceutical Co., Ltd., approval number: NMPN H11021391, usage and dosage: anal inserting of 100 mg at 0.5 hours after ERCP).

Table 1. Comparisons of baseline data of patients between two groups.

| Factors                  | Control group n=72 | Observation group n=67 | P    |
|-------------------------|--------------------|------------------------|------|
| Sex (Male/Female)       | 35/37              | 31/36                  | 0.915|
| Age (years)             | 25~70              | 25~75                  |      |
| Average age (years)     | 56.53±8.48         | 56.82±8.57             | 0.842|
| BMI (kg/m²)             | 24.23±1.15         | 24.56±1.17             | 0.096|
| Type of disease (n, %)  |                    |                        |      |
| Choledocholithiasis     | 36 (50.00)         | 32 (47.76)             | 0.793|
| Pancreatolithiasis      | 21 (29.17)         | 18 (26.87)             |      |
| Stricture of bile duct  | 10 (13.89)         | 9 (13.43)              |      |
| Pancreatic tumor        | 5 (6.94)           | 8 (11.94)              |      |
Detection of related indicators

Venous blood (5 mL) was collected from each patient at 3 hours, 12 hours and 24 hours before and after ERCP, respectively followed by isolation of serum which was used to measure the levels of tumor necrosis factor-alpha (TNF-α), interleukin-6 (IL-6) and IL-8 by enzyme-linked immunosorbent assay (ELISA) in strictly accordance with the instructions of the relevant kit (produced by Thermo Fisher Scientific, USA).

Evaluation criteria

At 3 hours, 12 hours, and 24 hours before and after ERCP, the degree of abdominal pain in each patient was assessed through visual analogue scale (VAS). The score range was 0 to 10 points (0 point: painless, and 10 points: insufferable severe pain), and the score was positively correlated with the degree of pain.

Diagnostic criteria for post-ERCP pancreatitis [7] was: post-ERCP serum amylase level was over 3 times than the normal level, and abdominal pain or abdominal pain exacerbation lasted for more than 24 hours. Diagnostic criteria for hyperamylasemia [8] was: serum amylase level of the patient was higher than normal level for 12 consecutive hours after ERCP without obvious symptoms of abdominal pain.

Statistical analysis

Statistical Product and Service Solutions (SPSS) 19.0 software (SPSS Inc., Chicago, IL, USA) was used for data processing. Measurement data were expressed as mean ± standard deviation (SD), and t-test was employed for comparison of measurement data. Enumeration data were expressed as ratio (%) and compared by chi-square test. \( P<0.05 \) suggested that the difference was statistically significant.

Results

Comparisons of serum amylase level

At 3 hours after ERCP, serum amylase level in both groups started to increase. However, at 24 hours after ERCP, serum amylase level in observation group was decreased to the level before ERCP, which was significantly lower than that in control group \( (P<0.05) \) (Table 2).

Comparisons of levels of TNF-α, IL-6 and IL-8

There were no significant differences in serum levels of TNF-α, IL-6, and IL-8 before ERCP between the 2 groups \( (P>0.05) \). However, the levels after ERCP were significantly elevated, with more increases in the control group compared to the observation group \( (P<0.05) \) (Tables 3–5).

Comparisons of abdominal pain VAS scores

Post-ERCP pain scores of patients in both groups were significantly increased compared with those before ERCP, with more increases in the control group than those in the observation group \( (P<0.05) \) (Table 6).

Comparisons of incidence rates of complications after ERCP

In comparison with the control group, the observation group had significantly reduced incidence rates of post-ERCP pancreatitis and hyperamylasemia \( (P<0.05) \) (Table 7).

Analyses of influential factors of post-ERCP pancreatitis

The transfusion was taken as a dependent variable, and the patient’s age, gender, difficult intubation, pancreatography, long surgery duration, history of previous pancreatitis, and nasobiliary drainage were used as independent variables. Logistic regression analyses showed that difficult intubation [odds ratio (OR)=2.315, \( P=0.005 \)], pancreatography (OR=3.936, \( P=0.007 \)), long surgery duration (OR=1.823, \( P=0.008 \)) and history of previous pancreatitis (OR=1.415, \( P=0.013 \)) were identified as independent risk factors affecting post-ERCP pancreatitis \( (P<0.05) \) (Table 8).

Discussion

Biliary and pancreatic diseases are usually treated by surgical operations [9]. At present, ERCP has become one of the
Table 3. Comparisons of TNF-α levels of patients at different time points between two groups (ng/L).

| Group          | Cases | Before ERCP | 3 h after ERCP | 12 h after ERCP | 24 h after ERCP |
|----------------|-------|-------------|----------------|-----------------|-----------------|
| Control group  | 72    | 1.15±0.54   | 3.68±0.75*     | 3.26±0.63*      | 2.94±0.56*      |
| Observation group | 67    | 1.16±0.53   | 2.79±0.63*     | 2.52±0.52*      | 2.29±0.48*      |

Compared with that before ERCP, * P<0.05.

Table 4. Comparisons of IL-6 levels of patients at different time points between two groups (ng/L).

| Group          | Cases | Before ERCP | 3 h after ERCP | 12 h after ERCP | 24 h after ERCP |
|----------------|-------|-------------|----------------|-----------------|-----------------|
| Control group  | 72    | 10.63±3.62  | 74.89±5.63*    | 108.83±6.33*    | 61.83±5.27*     |
| Observation group | 67    | 10.36±3.24  | 63.84±5.84*    | 81.75±6.45*     | 32.75±5.13*     |

Compared with that before ERCP, * P<0.05.

Table 5. Comparisons of IL-8 levels of patients at different time points between two groups (ng/L).

| Group          | Cases | Before ERCP | 3 h after ERCP | 12 h after ERCP | 24 h after ERCP |
|----------------|-------|-------------|----------------|-----------------|-----------------|
| Control group  | 72    | 10.89±3.75  | 74.89±5.63*    | 108.83±6.33*    | 61.83±5.27*     |
| Observation group | 67    | 10.36±3.24  | 63.84±5.84*    | 81.75±6.45*     | 32.75±5.13*     |

Compared with that before ERCP, * P<0.05.

Table 6. Comparisons of abdominal VAS scores of patients before and after ERCP between two groups [point(s)].

| Group          | Cases | Before ERCP | 3 h after ERCP | 12 h after ERCP | 24 h after ERCP |
|----------------|-------|-------------|----------------|-----------------|-----------------|
| Control group  | 72    | 1.15±0.54   | 3.68±0.75*     | 3.26±0.63*      | 2.94±0.56*      |
| Observation group | 67    | 1.16±0.53   | 2.79±0.63*     | 2.52±0.52*      | 2.29±0.48*      |

Compared with that before ERCP, * P<0.05.

Table 7. Comparisons of incidence rates of post-ERCP pancreatitis and hyperamylasemia in patients between two groups (n, %).

| Group          | Cases | Pancreatitis | Hyperamylasemia |
|----------------|-------|--------------|-----------------|
| Control group  | 67    | 4 (5.97)     | 9 (13.43)       |
| Observation group | 72    | 15 (20.83)   | 26 (36.11)      |

χ² = 5.298, P = 0.021; 8.309, P = 0.004.
Due to personal factors of patients, for example, history of previous pancreatitis and difficult intubation corporeity, the incidence rate of post-ERCP pancreatitis will also be greatly increased. During ERCP, double-guidewire method is adopted for catheterization, namely, catheterization is done by implanting pancreatic duct guidewire first to straighten the duodenal ampulla and then to insert bile duct guidewire for intubation, which successfully solves the difficult intubation in patients and improves intubation rate. During surgical treatment, the incidence risk of post-ERCP pancreatitis will be increased if the surgery duration is over 1 hour, which requires the performer to improve the operating level of surgery to reduce the surgery duration as possible, thereby decreasing the incidence rate of post-ERCP pancreatitis.

TNF-α is the earliest and most central inflammatory mediator produced in the body, which can initiate and trigger inflammatory responses, leading to damages to organs or tissues [15]. IL-6 is an acute phase response multi-functional circulating lymphocyte factor that is composed of polypeptide glycoproteins and plays various roles (promoting and resisting inflammatory responses) in immune response, and the massive release of IL-6 is a dangerous signal [16]. IL-8 is a chemokine that is capable of activating neutrophils and participates in neutrophil-mediated damage [17]. Activation of a large number of inflammatory factors can cause a cascade of inflammatory reactions, thereby increasing the occurrence risk of post-ERCP pancreatitis [18]. Clinically, post-ERCP pancreatitis is prevented mainly from anti-inflammation drugs. In this study, octreotide combined with non-steroidal anti-inflammatory drugs was used for the prevention of post-ERCP pancreatitis, and results indicated that post-ERCP serum amylase level was significantly increased; together with increased levels of TNF-α, IL-6 and IL-8 and VAS scores in both groups. However, the increases in the control group were significantly more than those observed in the observation group. This might be because octreotide is a synthetic derivative of natural somatostatin, which directly inhibits the secretion of pancreatic enzyme, indirectly suppresses the secretion of pancreatic enzyme gastrin, and

Table 8. Logistic regression analyses on factors influencing post-ERCP pancreatitis.

| Factors                        | B     | S.E   | Wald  | OR   | 95% CI          | P     |
|-------------------------------|-------|-------|-------|------|-----------------|-------|
| Age                           | 0.331 | 0.512 | 2.783 | 0.723 | 0.475–0.952     | 0.105 |
| Sex                           | -0.437| 0.507 | 2.372 | 0.253 | 0.107–0.759     | 0.153 |
| Difficult intubation          | 0.867 | 0.673 | 5.421 | 2.315 | 1.106–3.854     | 0.005 |
| Pancreatography               | 0.635 | 0.714 | 6.425 | 3.936 | 1.396–6.542     | 0.007 |
| Long surgery duration         | 0.726 | 0.649 | 5.753 | 1.823 | 1.075–3.212     | 0.008 |
| History of previous pancreatitis | 0.633 | 0.817 | 5.524 | 1.415 | 1.103–2.347     | 0.013 |
| Nasobiliary drainage          | 0.315 | 0.486 | 3.292 | 0.546 | 0.125–0.973     | 0.208 |
ultimately reduces the secretion in the pancreas, relaxing Oddi sphincter, thereby relieving post-ERCP abdominal pain and promoting the recovery of serum amylase [19]. Indomethacin is a non-steroidal anti-inflammatory drug, which can effectively inhibit the cascade reaction of inflammation, and reduce the secretions of TNF-α, IL-6 and IL-8, thereby protecting pancreatic parenchyma cells [20].

Conclusions

Difficult intubation, pancreatography, long surgery duration, and history of previous pancreatitis were identified as the risk factors for post-ERCP pancreatitis, and the incidence of post-ERCP pancreatitis was shown to be reduced through administration of octreotide combined with non-steroidal anti-inflammatory drugs.

Conflict of interest

None.

References:

1. Facchiano E, Quartararo G, Pavoni V: Laparoscopy-assisted transgastric endoscopic retrograde cholangiopancreatography (ERCP) after Roux-en-Y gastric bypass: Technical features. Obes Surg, 2015; 25(2): 373–76
2. Mai W A, Shal SME, Sombaty AIE: Propofol dexmedetomidine versus propofol ketamine for anesthesia for endoscopic retrograde cholangiopancreatography (ERCP) (A randomized comparative study). Egyptian Journal of Anaesthesia, 2015; 31(2): 97–105
3. Rustagi T, Jamidar PA: Endoscopic retrograde cholangiopancreatography (ERCP)-related adverse events: post-ERCP pancreatitis. Gastrointest Endosc Clin N Am, 2015, 25(1): 107–21
4. Chu LP, Zhou JJ, Yu YF et al: Clinical effects of pulse high-volume hemofiltration on severe acute pancreatitis complicated with multiple organ dysfunction syndrome. Ther Apher Dial, 2013; 17(1): 78–83
5. Sutherland DER, Radosievich DM, Bellin MD et al: Total pancreatectomy and islet autotransplantation for chronic pancreatitis. Abdominal Radiology, 2015; 214(7): 409–24
6. Yang JF, Farooq P, Zwilling K: Efficacy and safety of propofol-mediated sedation for outpatient endoscopic retrograde cholangiopancreatography (ERCP). Dig Dis Sci, 2016; 61(7): 2146–46
7. Riesco JM, Perez-Miranda M, González-Huix F: Sa1179 high compliance with guideline recommendations on post-ercp pancreatitis (PEP) prevention is associated with low pep incidence: Results from a national Spanish survey. Gastrointestinal Endoscopy, 2016; 83(5): A8244
8. Fujita Y, Hasegawa S, Kato Y: Intravenous injection of low-dose flurbiprofen axetil for preventing post-ERCP pancreatitis in high-risk patients: An interim analysis of the study. Endosc Int, 2016; 4(10): E1078
9. Omar MA, Ahmed AE, Said OA: Risk factors for post ERCP pancreatitis: A prospective multicenter study in Upper Egypt. Egyptian Journal of Surgery, 2015; 34(1): 1–10
10. Hashimoto S, Ito K, Koshiba S: Risk factors for post-endoscopic retrograde cholangiopancreatography (ERCP) pancreatitis and stent dysfunction after preoperative biliary drainage in patients with malignant biliary stricture. Intern Med, 2016; 55(18): 2529–36
11. Hassan HIEA: Dexmedetomidine versus ketofol for moderate sedation in Endoscopic retrograde cholangiopancreatography (ERCP) comparative study. Egyptian Journal of Anaesthesia, 2015; 31(1): 15–21
12. Hazey JW: Commentary Re: Meta-analysis of early endoscopic retrograde cholangiopancreatography (ERCP) ± endoscopic sphincterotomy (ES) versus conservative management for gallstone pancreatitis (GSP). Surg Laparosc Endosc Percutan Tech, 2015; 25(3): 185–203
13. Bekkali N, Thomas T, Murray S: PWE-161 Preventing post-ERCP pancreatitis (PEP): The role of prophylactic pancreatic duct stenting in the rectal NSAID era. Gut, 2016; 65(Suppl. 1): A217
14. Adams HL, Jaunoo SS: PTU-017 An audit of post ercp pancreatitis (pep) over four years in a UK tertiary centre. Gut, 2015; 64(Suppl. 1): A65
15. Murdaca G, Spanò F, Contatore M et al: Infection risk associated with anti-TNF-α agents: A review. Expert Opin Drug Saf, 2015; 14(4): 571–82
16. Pedersen BK, Febrero M: Exercise and interleukin-6 action. Expert Review of Endocrinology & Metabolism, 2014; (3): 319–21
17. Beigelman A, Isaacsenschm M, Sajol G: Randomized trial to evaluate azithromycin’s effects on serum and upper airway IL-8 levels and recurrent wheezing in infants with respiratory syncytial virus bronchiolitis. J Allergy Clin Immunol, 2015; 135(5): 1171–78
18. Mariani A, Di LM, Giardullo N: Early precut sphincterotomy for difficult biliary access to reduce post-ERCP pancreatitis: A randomized trial. Endoscopy, 2015; 48(06): 530–35
19. Poincloux L, Rouquette O, Buco: Endoscopic ultrasound-guided biliary drainage after failed ERCP: Cumulative experience of 101 procedures at a single center. Endoscopy, 2015; 47(9): 794–801
20. Martínez-Granero F, Rivilla R, Martín M: Diclophenac potassium versus celebrex in the prophylaxis of post-ERCP pancreatitis: A randomized trial. Endoscopy, 2015; 47(9): 794–801

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