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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, including10 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/m^2)	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)	

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Table 2. Comparisons of serum amylase level of patients before and after ERCP between two groups (U/L).

Group	Cases	Before ERCP	3 h after ERCP	12 h after ERCP	24 h after ERCP
Control group	72	95.86±11.76	183.27±13.68*	238.75±16.45*	162.75±15.13*
Observation group	67	95.72±11.98	138.65±12.62*	182.83±16.34*	101.63±15.28
P		0.944	<0.001	<0.001	<0.001

Compared with that before ERCP, * $P<0.05$.

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

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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	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*
P		0.645	<0.001	<0.001	<0.001

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	35.69±4.63	156.79±9.63*	193.83±12.36*	182.43±8.28*
Observation group	67	34.74±4.23	123.64±9.67*	148.62±11.75*	120.56±8.27*
P		0.210	<0.001	<0.001	<0.001

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	40.56±3.75	197.68±13.48*	267.94±19.23*	224.39±14.48*
Observation group	67	40.78±3.68	168.28±10.42*	203.36±17.38*	157.84±9.53*
P		0.728	<0.001	<0.001	<0.001

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*
P		0.913	<0.001	<0.001	<0.001

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)
χ^2		5.298	8.309
P		0.021	0.004

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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

existing main approaches for the diagnosis and treatment of biliary and pancreatic diseases. Moreover, the success rate of ERCP has reached up to 90% [10]. ERCP is an invasive procedure, and there are complications (infection, perforation, bleeding, etc.) after ERCP. Among the complications, hyperamylasemia and pancreatitis commonly occur, with an occurrence rate of 40% [11]. Generally, the consequence of hyperamylasemia is not serious, and the patient usually returns to normal within 24 to 48 hours after ERCP; however, it still increases the psychological burden on the patients, and might even develop into acute pancreatitis if intervention is not carried out on time [12]. Currently, the pathogenesis of post-ERCP pancreatitis remains poorly understood and is generally believed to be directly related with personal factors of patients and surgical procedures, and might be a pathological consequence caused by infection, mechanical and chemical injuries, etc. The specific mechanism is demonstrated to be as follows: duodenal papilla edema, bile reflux, and Oddi sphincter spasm occur due to various factors, resulting in increased pressure in pancreatic ducts, abnormal secretion of pancreatic enzyme, and large aggregation of zymogen granules in acinar cells plus their fusion with lysosomes, eventually activating pancreatin zymogen in advance, and leading to damage to pancreatic parenchyma [13,14].

Logistic regression analyses in this study revealed that independent risk factors affecting post-ERCP pancreatitis included difficult intubation (OR=2.315), pancreatography (OR=3.936), long surgery duration (OR=1.823) and history of previous pancreatitis (OR=1.415) ($P<0.05$). Based on OR, it was found that pancreatography is the main risk factor for the occurrence of post-ERCP pancreatitis, which is affected by the injection speed and dosage of contrast agents. After contrast agents enter into the pancreatic duct, the static pressure is elevated, and cell-cell junction is destructed, leading to flowing back of pancreatic juice to the pancreatic parenchyma, which activates pancreatic enzymes, resulting in the phenomenon of self-digestion. Therefore, it is important to limit contrast agent dosage and pay attention to avoiding rapid injection in clinical practice. 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

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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.

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