Original Article
Clinical observation of octreotide combined with diclofenac sodium in preventing ERCP-related pancreatitis

Xian Zhou[1], Jianwu Long[1], Hui Wang[2], Shijie Yi[2], Jun Zhao[2]

Departments of [1]Hepatobiliary Surgery, [2]Gastrointestinal Surgery, Nanhua Hospital, Nanhua University, Hengyang, Hunan Province, China

Abstract: Objective: To elucidate the efficacy of octreotide in combination with diclofenac sodium in the prevention of ERCP-related pancreatitis, and investigate its impact on patients' serum amylase, white blood cell (WBC) count, adverse effects, hyperamylasemia and hemorheology. Methods: The prospective study was conducted, in which 124 patients who underwent endoscopic retrograde cholangiopancreatography (ERCP) in our hospital were evenly divided into 2 groups, the observation group (n=62) and the control group (n=62), via a random number table method. The control group was administered diclofenac sodium lidocaine hydrochloride via injection after ERCP, while the observation group was given octreotide acetate on the basis of the control group. The incidence of pancreatitis, serum amylase level, WBC count, incidence of adverse effects and hyperamylasemia, and hemorheology levels were compared between these two groups of patients. Results: The incidence of pancreatitis in the observation group was significantly lower than that in the control group (P<0.05). After treatment, the serum amylase level at 24 h post-surgery in the observation group was notably lower than that in the control group (P<0.001). The WBC count at 2 h and 24 h post-surgery in the observation group were both significantly lower than those in the control group (all P<0.001). The incidence of total adverse reactions in the observation group was remarkably lower than that in the control group (P<0.01). The incidence of hyperamylasemia in the observation group was considerably lower than that in the control group (P<0.001). Twenty-four hours post-surgery, the whole blood viscosity at high shear rate, whole blood viscosity at low shear rate, and plasma viscosity in the observation group were all significantly lower than those in the control group (all P<0.001). Conclusion: The combination of octreotide and diclofenac sodium could effectively prevent the occurrence of ERCP-related pancreatitis, which reduced the incidence of hyperamylasemia, decreased the WBC count and serum amylase level, improved the hemorheology, and lowered the incidence of adverse effects in patients after ERCP. Therefore, this therapeutic strategy is worthy of clinical propagation and application.

Keywords: Octreotide, diclofenac sodium, endoscopic retrograde cholangiopancreatography-related pancreatitis, hyperamylasemia

Introduction

Hepatobiliary and pancreatic diseases mainly refer to acute and chronic hepatitis, liver cirrhosis, fatty liver, cholecystitis, cholelithiasis, acute and chronic pancreatitis, tumors, etc.; which are digestive system diseases that are characterized by a high incidence and are difficult to diagnosed and be treated [1, 2]. Endoscopic retrograde cholangiopancreatography (ERCP) has been widely applied in clinical practice for the treatment of hepatobiliary and pancreatic diseases by taking advantage of

having lettle trauma and a quick recovery after surgery via ERCP [3]. However, repeated tracheal intubation during ERCP causes damage to the duodenal papilla and sphincter, leading to increased intra-pancreatic pressure and pancreatitis, of which the incidence ranges from 2% to 19.6%, and even up to 25% among high-risk patients. Some patients can develop severe pancreatitis, which causes pain and increases hospitalization and costs [4]. There are two major clinical prevention and therapeutic strategies to treat pancreatitis: non-drug and drug treatments. The non-drug strategy

Table 1. Comparison of general information between the two groups of patients (n, $\bar{x} \pm sd$)

Index	Observation group (n=62)	Control group (n=62)	χ^2/t	P
Age (years)	57.4±4.1	56.6±5.8	0.865	0.391
Gender (n)			0.032	0.857
Male	34	33		
Female	28	29		
BMI (kg/m^2)	22.75±2.15	22.50±3.01	0.532	0.596
ERCP surgery time (min)	49.55±7.12	50.53±8.80	0.682	0.497
Disease diagnosis (n)			0.260	0.878
Bile tube stones	27	28		
Obstructive jaundice	25	26		
Gallbladder disease	10	8		
Comorbid diseases (n)				
Hypertension (n)	15	13	0.053	0.818
Coronary heart disease (n)	11	9	0.238	0.625
Diabetes (n)	7	6	0.086	0.769
Smoking history (n)	9	7	0.287	0.592
Drinking history (n)	5	5	0.000	1.000
Underlying diseases (n)			1.940	0.857
Gallbladder stones	25	26		
Bile tube cancer	15	13		
Pancreatic head cancer	10	10		
Ampullary cancer	5	7		
Duodenal papilla cancer	5	3		
Duodenal papilla stenosis	2	3		

Note: ERCP: endoscopic retrograde cholangiopancreatography; BMI: body mass index.

will provide clinical practice guidelines for future studies and treatment.

Materials and methods

General information

By applying a prospective study, 124 patients who underwent ERCP in the Nanhua Hospital, at Nanhua University (March 8th, 2017 to August 12th, 2019) were recruited and divided into the observation group and the control group by random number table method, with 62 patients in each group. The general information of the two groups was listed in **Table 1**. This study was approved by the Ethics Committee of Nanhua Hospital, Nanhua University.

Inclusion criteria: (1) All patients were scheduled to undergo ERCP after the examination by B-ultrasound, CT or MRCP [7, 8]. (2) Serum amylase level was within the normal range before the surgery; (3) No contraindications and allergies to the drugs involved in this study; (4) Age ≥18 years; (5) Patients understood the purpose of this study and signed the informed consent.

Exclusion criteria: (1) Patients with pancreatitis or pancreatic tumor before the surgery; (2) Patients with severe heart, liver and/or kidney diseases; (3) Patients with ulcers, bleeding, perforation, and/or obstruction; (4) Patients with severe mental illness; (5) Patients with cognition dysfunction.

Methods

ERCP protocol: after the patient was anesthetized, a duodenoscope (Olympus Japan, TJF-260V) was inserted from the mouth into the middle of the duodenum to find the bile duct opening. Then, from the tip of the duodenoscope to the opening of the bile duct, unique

includes a plastic stent drainage, pancreatic duct stent implantation and so forth; which, can result in the imbalance of bile and electrolytes [5]. Studies have reported that octreotide can reduce the secretion of pancreatic enzymes, which has been used to effectively prevent post-ERCP pancreatitis (PEP). Diclofenac sodium, a non-steroidal anti-inflammatory drug (NSAID), can block the inflammatory cascade and effectively prevent the occurrence of PEP [6]. Currently, only a few studies have reported on the combination of octreotide and diclofenac sodium to prevent ERCP-related pancreatitis. Therefore, this study aimed to investigate the clinical efficacy of octreotide combined with diclofenac sodium in the prevention of ERCP-related pancreatitis, and analyze the effects on the serum amylase level, WBC count, incidence of adverse effects and hyperamylasemia, and hemorheology, which

guide wires and tools were inserted to fulfill the hepatobiliary system/pancreatic duct angiography (guide wires, nasal bile ducts, bare metal stents, plastic stents for bile ducts, and expansion balloons were all purchased from Boston, US), and related surgical treatments were performed at the same time. If the patient had a tumor, a specimen was collected for pathological analysis or kept on a biliary stent; if the patient had a stone, the stone was removed.

The control group was injected with 2 mL diclofenac sodium lidocaine hydrochloride immediately after the surgery (Mepha Holding AG, 2 mL: diclofenac sodium 75 mg and lidocaine hydrochloride 20 mg, 5 bottles/box).

The observation group was administered 0.1 mg diclofenac sodium and octreotide acetate (Beijing Baiao Pharmaceuticals Co., Ltd., China, 0.05 mg: 1 mL). Postoperative fasting was done for 24 h.

Outcome measures

Major outcome measures: (1) The incidence of pancreatitis was compared between the two groups. The diagnostic criteria for pancreatitis: postoperative hyperamylasemia with acute abdominal pain, upper abdominal tenderness, nausea, vomiting or acute pancreatitis by ultrasound, MRI, and CT. The length of hospital stay was evaluated as mild, moderate, and severe [9]. (2) The serum amylase levels of the two groups of patients were compared [10]. Twenty-four hours before and after the surgery, 5 mL of morning fasting venous blood was centrifuged at 4000 r/min for 5 min to separate serum, which was analyzed by an automatic biochemical analyzer (Xiamen Haifei Biotechnology Co., Ltd., BS-330). (3) The incidence of hyperamylasemia was compared between the two groups of patients. The diagnostic criteria: serum amylase levels 2-24 h after the surgery were greater than 3 times of the upper limit level without obvious clinical manifestations [11]. Hyperamylasemia occurrence rate = number of cases of hyperamylasemia/total number of cases × 100%.

Secondary outcome measures: (1) The white blood cell (WBC) count of the two groups of patients was compared. Briefly, 5 mL of peripheral venous blood samples was collected at 2 h and 24 h post-surgery in the early morning. A blood analyzer (Taiyuan Weikang Hongye Technology Co., Ltd., China, UniCel DxH 800) was used for detection. (2) The incidence of adverse effects such as nausea, vomiting, and dizziness between the two groups of patients were compared. If multiple complications occurred in the same patient, the multiple complications were counted when calculating the total incidence. The total incidence = number of complication cases/total number cases × 100%. (3) The hemorheology level of the two groups of patients was compared [12]. Twenty-four hours before and after the surgery, 5 mL of whole blood sample was collected in the morning, and an automatic hemorheology instrument (Shanghai Hanfei Medical Equipment Co., Ltd., China, N7500A) was used to analyze the whole blood viscosity at high shear rate, whole blood viscosity at low shear rate, and plasma viscosity.

Statistical analysis

SPSS 20.0 was applied for the data analysis. The counting data was expressed as n/% and analyzed via χ^2 test. Quantitative data that followed a normal distribution was expressed as mean ± standard deviation ($\overline{x}$ ± sd) and analyzed by independent t test for the data between groups or by paired t test for the data within the same group. If the data was not normally distributed, it was represented by the median and interquartile, and the rank sum test was carried out for the comparison between groups. $P < 0.05$ indicated a statistically significant difference.

Results

General information of the two groups of patients

There were no statistically significant differences in terms of the age, gender, body mass index (BMI), ERCP surgery time, disease diagnosis, comorbid diseases, smoking and drinking history, and underlying diseases between the two groups of patients (all P>0.05). Thus, the two groups were comparable (**Table 1**).

Incidence of pancreatitis in the two groups of patients

The incidence of pancreatitis in the observation group was significantly lower than that in the control group (P<0.05; **Table 2**).

Table 2. Comparison of the incidence of pancreatitis between the two groups of patients (n, %)

Group	Mild	Moderate	Severe	Incidence
Control group (n=62)	5 (8.06)	3 (4.84)	2 (3.23)	10 (16.13)
Observation group (n=62)	3 (4.84)	0 (0.00)	0 (0.00)	3 (4.84)
χ^2				4.211
P				0.040

Table 3. Comparison of serum amylase between the two groups of patients before and after treatment (U/L, $\bar{x} \pm sd$)

Group	Before treatment	24 h post-surgery
Control group (n=62)	51.42±11.19	105.44±22.20***
Observation group (n=62)	51.39±11.23	73.38±20.13***
t	0.015	8.424
P	0.988	<0.001

Note: Compared with before treatment, ***$P<0.001$.

Table 4. Comparison of white blood cell count between the two groups of patients after treatment (10^9/L, $\bar{x} \pm sd$)

Group	2 h post-surgery	24 h post-surgery
Control group (n=62)	13.37±0.43	7.54±0.30***
Observation group (n=62)	11.29±0.42	6.72±0.53***
t	27.247	10.602
P	<0.001	<0.001

Note: Compared with 2 h post-surgery, ***$P<0.001$.

Table 5. The occurrence of adverse effects in the two groups of patients (n, %)

Group	Nausea	Vomiting	Dizziness	Total adverse effects
Control group (n=62)	3 (4.84)	5 (8.06)	3 (4.84)	11 (17.74)
Observation group (n=62)	1 (1.61)	1 (1.61)	0 (0.00)	2 (3.23)
χ^2				6.960
P				0.008

Serum amylase levels after the treatment in the two groups of patients

Before treatment, the serum amylase levels of the two groups were not significantly different (P>0.05); after treatment, the serum amylase levels of the two groups were significantly higher than those of before treatment. Of note, the serum amylase level was notably lower in the observation group at 24 h post-surgery compared with the control group (all P<0.001; **Table 3**).

The WBC count of the two groups of patients after treatment

After treatment, the WBC counts of the patients at 24 h post-surgery in the two groups were significantly lower than those at 2 h post-surgery. The WBC count in the observation group was significantly lower than that in the control group at both 2 h and 24 h post-surgery (all P<0.001; **Table 4**).

The incidence of adverse effects in the two groups of patients

The incidence of total adverse effects in the observation group was significantly lower than that in the control group (P<0.01; **Table 5**).

The incidence of hyperamylasemia in the two groups

The incidence of hyperamylasemia in the observation group was significantly lower than that in the control group (χ^2= 17.0690, P<0.001; **Figure 1**).

Comparison of changes of hemorheology between the two groups of patients

Before treatment, there was no significant difference regarding the changes of whole blood viscosity at high shear rate, whole blood viscosity at low shear, and plasma viscosity between the two groups (P>0.05), while after the surgery the three indices of hemorheology in the observation group were significantly lower than those in the control group (all P<0.001; **Table 6**).

Discussion

The ERCP technique includes the insertion of a duodenoscope into the descending part of the duodenum to find the duodenal papilla, the
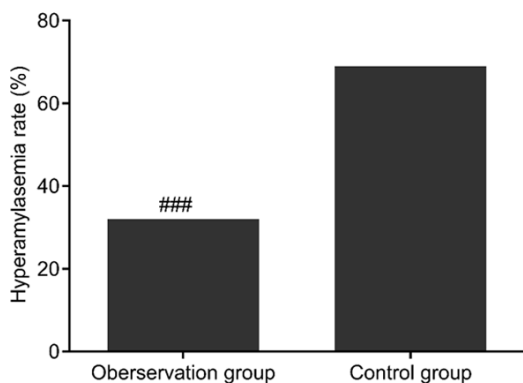
Figure 1. Comparison of the incidence of hyperamylasemia between the two groups of patients. Compared with the control group, ###$P<0.001$.

insertion of an artificial imaging catheter from the biopsy tube to the opening of the nipple, and the injection of the contrast agent to conduct an X-ray to image the pancreaticobiliary duct [13]. ERCP technique was developed in the late 1960s. In 1968, it was first reported that ERCP could successfully display the structure of the pancreaticobiliary duct to diagnose common bile duct stones, benign and malignant biliary obstruction, pancreatic biliary obstruction and other pancreaticobiliary diseases [14]. In 1974, a study found that a duodenal papillary sphincterotomy was feasible under ERCP, which has been widely used gradually in the minimally invasive treatment and the diagnosis of hepatobiliary and pancreatic diseases [15]. Studies have found complications such as pancreatitis, bleeding after sphincterotomy, infectious diseases, and gastrointestinal perforation after ERCP [16]. Clinical medication for pancreatitis mainly include the following four types: relief of the spasm of the Oddi sphincter; reduction of the secretion of pancreatic enzymes; blockage of the inflammatory cascade; inhibition of the activation of trypsin in the acinar [17].

Serum amylase is a glycoside hydrolase that is mainly derived from the pancreas, whose activity analysis is used for the diagnosis of acute pancreatitis. Studies have found that patients with pancreatitis have shown a significant increase in blood amylase, which is considered as a sensitive and specific diagnostic marker [18]. Studies have reported that octreotide has a protective effect on the pancreatic parenchymal cell membrane and inhibits the secretion

of pancreatin and insulin [19]. Liu Bangguo et al. have demonstrated that octreotide adjuvant treatment of acute pancreatitis can significantly improve the clinical efficacy and reduce the level of serum amylase based on the study of the clinical effect of octreotide adjuvant treatment in 168 patients with acute pancreatitis [20]. Diclofenac sodium, a non-steroidal anti-inflammatory drug (NSAID), typically has analgesic, anti-inflammatory and antipyretic effects, which exerts its function by inhibiting cyclooxygenase and blocking the synthesis of prostaglandins [21]. Hu Cui et al. recruited 120 patients undergoing ERCP and divided them into the observation group that was given an intramuscular injection of diclofenac sodium and compared them with the control group [22]. Their data has revealed that PEP and the rate of hyperamylasemia in the observation group was lower than that of the control group, suggesting that diclofenac sodium has the effect of preventing the occurrence of PEP. In this study, the two drugs mentioned above have been used together to explore the synergistic effects on the ERCP-related pancreatitis. Our results have shown that the incidence of pancreatitis in the observation group was significantly lower than that in the control group, which suggests that the combination of octreotide and diclofenac sodium can reduce the incidence of pancreatitis in comparison to a single medication and indicates the advantages of the combined medication strategy. This study has also demonstrated that the combined medication can reduce the serum amylase level and the incidence of hyperamylasemia.

Leukocytes are very important in the blood system, which function through the phagocytosis of foreign invaders, producing antibodies, resisting the invasion of pathogens, playing a role in the wound healing, etc. Studies have found that the peripheral blood WBC count is relatively high in patients with pancreatitis, which can predict the severity of acute pancreatitis [23]. Our data has found that the WBC count of the observation group was significantly lower than that of the control group, which indicated that the combination of octreotide and diclofenac sodium can reduce the WBC count more effectively compared with the treatment via single medication. This may be explained by the application of the octreotide in the observation group that can reduce the

Table 6. Complications of the two groups of patients (mPa/s, $\bar{x} \pm sd$)

Group	Whole blood viscosity at high shear rate		Whole blood viscosity at low shear rate		Plasma viscosity	
	Before treatment	24 h post-surgery	Before treatment	24 h post-surgery	Before treatment	24 h post-surgery
Control group (n=62)	6.39±1.28	5.37±0.77	12.97±1.22	7.82±1.08	1.78±0.41	1.42±0.08
Observation group (n=62)	6.58±1.19	4.56±0.89	12.74±1.67	5.02±1.17	1.71±0.24	0.99±0.11
t	0.856	5.419	0.876	13.846	1.160	24.893
P	0.394	<0.001	0.383	<0.001	0.249	<0.001

production of multiple inflammatory factors, induce the apoptosis of inflammatory cells, and thereby prevent the aggregation of WBCs, leading to the downregulation of the WBC count.

Studies have reported that the main adverse effects of octreotide occur in the gastrointestinal track, including anorexia, vomiting, abdominal cramps, pain, nausea, diarrhea, etc., while the main adverse effects of diclofenac include gastrointestinal symptoms (acid reflux, nausea, vomiting), nervous system disorders (dizziness, headache, drowsiness, etc.), lower extremity edema, electrolyte disturbances, additionally, some patients may have elevated transaminase levels, rash, jaundice, neutropenia or thrombocytopenia, and arrhythmia [24, 25]. This study has investigated the incidence of adverse effects in the two groups of patients, in which the incidence of adverse effects in the observation group was significantly lower than that in the control group. Our data suggests that the combination of octreotide and diclofenac sodium can effectively and safely prevent the pancreatitis after ERCP.

Studies have also shown that octreotide can stimulate the hepatic reticuloendothelial system and improve the hemorheology of patients [12]. Finally, the effects of combined treatment on the hemorheology of patients has also been investigated. Our study has found that the levels of the three hemorheology indicators in patients in the observation group were significantly lower than those of the control group, which indicates that the combination of medication is beneficial to maintain the patients' normal hemorheology state. This effect may be due to the fact that octreotide inhibits platelet activity and improves the patients' microcirculation state. However, the mechanism by which octreotide improves hemorheology is beyond the scope of this study. In addition, a large cohort investigation warrants future studies.

In summary, the combination of octreotide and diclofenac sodium effectively prevented the occurrence of ERCP-related pancreatitis, which reduced the incidence of hyperamylasemia, decreased the WBC count and serum amylase level, improved the hemorheology, and lowered the incidence of adverse effects in patients after ERCP. Therefore, this therapeutic strategy is worthy of clinical application.

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Disclosure of conflict of interest

None.

Address correspondence to: Jun Zhao, Department of Gastrointestinal Surgery, Nanhua Hospital, Nanhua University, No. 336 Dongfeng South Road, Zhuhui District, Hengyang 421002, Hunan Province, China. Tel: +86-0734-8358047; E-mail: zhaojun336x@163.com

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