Submitted: 23 March, 2023 Accepted: 06 June, 2023 Published: 08 September, 2023 DOI:10.22514/sv.2023.090

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ORIGINAL RESEARCH

Comparison of octreotide and proton pump inhibitor in the prevention of acute pancreatitis after endoscopic retrograde cholangiopancreatography for different diseases

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Abstract

This study compared the role of octreotide and proton pump inhibitor (PPI) in preventing acute pancreatitis after endoscopic retrograde cholangiopancreatography (ERCP). The 320 patients who received ERCP from January 2019 to June 2022 were randomly and evenly divided into octreotide, PPI, combined treatment and control groups. The incidence of post-ERCP acute pancreatitis (PEP) and hyperamylasemia was counted. The incidence of PEP and hyperamylasemia after surgery differed significantly among all groups. For incidence of PEP, it was similar in the control, octreotide and PPI groups (12.50%, 8.75% and 10.00%), all of which were higher than that of the combined treatment group (1.25%). The incidence of hyperamylasemia was similar between the octreotide and PPI groups (12.50% and 13.75%), both decreased compared with the control group (32.50%), and further lowered in the combined treatment group (8.75%), and all differences were statistically significant ($p < 0.05$). For patients with choledocholithiasis, the incidence of hyperamylasemia in the combined treatment group was lower than that in the other three groups (8.33%, 31.25%, 21.43% and 16.67%) after intervention, while there were no significant differences in the incidence of PEP and hyperamylasemia in patients with cholangiocarcinoma, pancreatic head carcinoma and other lesions. In conclusion, preoperative application of octreotide or PPI alone has a slight effect on preventing PEP and hyperamylasemia after ERCP, and their combination is dramatically effective in preventing PEP.

Keywords

ERCP; Acute pancreatitis; Hyperamylasemia; Octreotide; PPI

1. Introduction

Endoscopic retrograde cholangiopancreatography (ERCP) is an important means for the treatment of hepatobiliary and pancreatic diseases, but it is invasive and may cause various complications, among which post-ERCP pancreatitis (PEP) is very common [1–4]. Studies have shown that the incidence of PEP ranges from 1% to 24%, and death may by caused by severe PEP, posing a great medical burden. Therefore, it is a research hotspot to increase the safety of ERCP and avoid PEP [5–7]. Pharmacological interventions are an important tool to prevent PEP. By reducing the level of pancreatic enzymes in the pancreas, it prevents the local fusion of pancreatic enzymes with lysosomes, thus blocking the inflammation storm due to activated pancreatic enzymes and decreasing the postoperative pressure of sphincter of Oddi [8–10]. Octreotide is an artificial analogue of somatostatin, which shares similar functions with somatostatin. The two of them is able to inhibit the secretion of pancreatic enzymes [11–13]. Proton pump inhibitors (PPIs) work similarly with H2 receptor blockers in the inhibition of PEP by suppressing gastric acid secretion and reducing pancreatic juice and pancreatic enzyme secretion induced by acid stimulation [14, 15]. To investigate the function of octreotide and PPIs in the prevention of PEP and hyperamylasemia after ERCP, the present study was conducted as follows.

2. Materials and methods

2.1 Study objects

The 320 patients who received ERCP from January 2019 to June 2022 were included in this study. (1) Inclusion criteria: patients were no less than 18 years old; patients' ERCP was completed by the same crew of medical workers; patients' indices of blood routine examination and routine urine test, and the level of hemodiastase and coagulation function were normal. (2) Exclusion criteria: patients had pancreatitis before; patients did not complete the procedure for various reasons; patients did not undergo relevant examinations on time after

treatment. (3) Case data: patients were randomly and evenly divided into octreotide, PPI, combined treatment and control groups. The general data of the four groups were not significantly different ($p > 0.05$). See Table 1.

2.2 Methods

2.2.1 Preoperative prophylactic drug regimens

Drug interventions were performed two hours before surgery. In octreotide group, a dose of 0.6 mg of octreotide in a 48 mL of saline was used; in PPI group, a dose of 40 mg of esomeprazole was used; in combined treatment group, the same doses of these two drugs were used; in control group, the same amount of saline was used. All the liquids were continuously and intravenously given using a micropump.

2.2.2 Examination and treatment by ERCP

An Electronic duodenoscope (Olympus TGF260, Tokyo, Japan) was used in this study. All patients should complete preoperative examinations for ERCP. They were fasted for 8 h before surgery and injected with 10 mg of scopolamine, 10 mg of diazepam, and 50 mg of pethidine hydrochloride intramuscularly 30 min before surgery to increase their surgical endurance. A volume of 8–10 mL of Dacromet Hydrochloride Gel Paste was administered 10 min before surgery to narcotize the larynx, lubricate the pharynx and eliminate bubbles during operation. The patient was placed in the left prone position with the head tilted to the right for the establishment of an intravenous fluid line. Then, they were given oxygen and monitored by electrocardiogram and oxygen saturation. Intraoperatively, diagnosis and related treatment of ERCP were performed according to relevant standards. Postoperatively, patients were fasted for 24 h. At 4 h, 24 h and 48 h after surgery, indices of blood routine examination and the level of hemodiastase were measured. Then, based on the results of the examination, the patients were treated with anti-inflammatory, hepatoprotective and enzyme-suppressive therapy.

2.3 Postoperative diagnosis of PEP and hyperamylasemia [16]

Patients were diagnosed with postoperative PEP if pancreatitis-related pains including abdominal pain, nausea, vomiting and epigastric tenderness happened after ERCP, with symptoms lasting more than 24 h and postoperative hemodiastase levels exceeded their normal levels by more than three times. The side effects of patients could be classified as mild (hospitalized for less than 3 days without systemic complications), moderate (hospitalized for 3–10 days without systemic complications) and severe (hospitalized for more than 10 days with local or systemic complications). Hyperamylasemia was considered in the case of hemodiastase levels were above the normal range but no pancreatitis-related pains occurred.

2.4 Statistics

SPSS 19.0 statistical software (IBM, Armonk, NY, USA) was used to process the data. The measurement data were expressed as ($\bar{x} \pm s$), and independent sample t-test was used for analysis. The categorical data were expressed as proportion, and χ^2 test was adopted for comparison between groups. A p value ≤ 0.05 was considered statistically significant.

3. Results

3.1 Hemodiastase levels in the four groups

Hemodiastase levels varied significantly among all groups at postoperative 4 h, 24 h and 48 h ($p < 0.05$), which were significantly decreased in the octreotide, PPI and combined treatment groups at all-time points compared with control group, but similar between the first two groups. Hemodiastase levels were the lowest in the combined treatment groups shown in Table 2.

3.2 Incidence of postoperative PEP and hyperamylasemia in the four groups

The incidence of PEP and hyperamylasemia after surgery differed significantly among all groups ($p < 0.05$). The combined treatment group exhibited the lowest incidence of PEP. Compared with the control group, the incidence of hyperamylasemia significantly decreased in the octreotide, PPI and combined treatment groups ($p < 0.05$), as shown in Table 3.

3.3 Incidence of postoperative PEP and hyperamylasemia in four groups of patients with different disease types

For patients with choledocholithiasis, the incidence of hyperamylasemia in the combined treatment group was significantly lower than that in the other three groups after intervention with different drugs ($p < 0.05$), while there were no significant differences in the incidence of PEP and hyperamylasemia in patients with cholangiocarcinoma, pancreatic head carcinoma and other lesions after intervention ($p > 0.05$) as shown in Table 4.

4. Discussion

ERCP in the clinical management of hepatobiliary and pancreatic diseases is significant important, but prevention of postoperative PEP is an important prerequisite to ensure the safety of ERCP [17–19]. Complicated causes are involved in the occurrence of PEP after ERCP, which are mainly associated with the following factors [20–25]: (1) repeated intubation during ERCP causes papillary injury and edema, resulting in obstruction of biliopancreatic fluid outflow; (2) injury to the opening of the pancreatic duct due to incision of the duodenum causes edema of the surrounding mucosal tissue; (3) contaminated endoscope leads to contamination in the intestinal tract; (4) overdose of contrast agent results in increased pressure in the pancreatic duct and its toxicity causes damage to the pancreatic alveoli. For the above pathogenesis, the prevention of PEP after ERCP is mainly classified into technical prevention and pharmacological prevention, of which technical prevention mainly includes: (1) improving the operator's surgical skills to avoid intraoperative local tissue injury; (2) selective appli-

TABLE 1. General data of patients from the four groups.

Group	n	Male/ Female	Age (yr)	Type of diseases (n, %)				Type of ERCP (n, %)	
				Choledoch-olithiasis	Cholangio-carcinoma	Pancreatic head carcinoma	Others	Diagnostic ERCP	Therapeutic ERCP
Control	80	48/32	56.33 ± 14.58	58 (72.50)	16 (20.00)	6 (7.50)	0 (0.00)	29 (36.25)	51 (63.75)
Octreotide	80	52/28	57.58 ± 15.33	52 (65.00)	14 (17.50)	10 (12.50)	4 (5.00)	30 (37.50)	50 (62.50)
PPI	80	44/36	56.63 ± 13.87	56 (70.00)	18 (22.50)	4 (5.00)	2 (2.50)	28 (35.00)	52 (65.00)
Combination	80	46/34	57.94 ± 14.66	50 (62.50)	12 (15.00)	12 (12.50)	6 (7.50)	31 (38.75)	49 (61.25)
F/χ^2		1.814	0.218	13.701				0.269	
p		0.612	0.884	0.132				0.966	

PPI: proton pump inhibitor; ERCP: endoscopic retrograde cholangiopancreatography.

TABLE 2. Hemodiastase levels in the four groups ($\bar{x} \pm s$, U/L).

Group	n	Postoperative 4 h	Postoperative 24 h	Postoperative 48 h
Control	80	253.69 ± 22.48	261.15 ± 26.54	233.25 ± 27.79
Octreotide	80	163.77 ± 16.89^{a}	143.69 ± 20.05^{a}	113.25 ± 16.89^{a}
PPI	80	167.41 ± 17.73^{a}	145.78 ± 16.54^{a}	116.41 ± 17.33^{a}
Combination	80	135.56 ± 18.33^{abc}	129.48 ± 13.97^{abc}	101.15 ± 12.08^{abc}
F		612.571	760.837	813.777
p		<0.001	<0.001	<0.001

Note: Compared with control group, $^{a}p < 0.05$; compared with octreotide group, $^{b}p < 0.05$; compared with PPI group, $^{c}p < 0.05$. PPI: proton pump inhibitor.

TABLE 3. Incidence of postoperative PEP and hyperamylasemia in the four groups (n, %).

Group	n	PEP	Hyperamylasemia
Control	80	10 (12.50)	26 (32.50)
Octreotide	80	7 (8.75)	$10 (12.50)^{a}$
PPI	80	8 (10.00)	$11 (13.75)^{a}$
Combination	80	$1 (1.25)^{abc}$	$7 (8.75)^{a}$
χ^2		7.535	19.337
p		<0.001	<0.001

Note: Compared with control group, $^{a}p < 0.05$; compared with octreotide group, $^{b}p < 0.05$; compared with PPI group, $^{c}p < 0.05$. PEP: post-ERCP acute pancreatitis. PPI: proton pump inhibitor.

cation of endoscopic nasal bile drainage (ENBD), endoscopic retrograde pancreatic drainage (ERPD), *etc.* to ensure the smooth drainage of bile, pancreatic fluid and contrast agent, and to avoid the formation of intrapancreatic ductal hypertension. Compared with technical prevention, pharmacological prevention is more achievable in clinical practice. Several modalities have been investigated, the drugs for prevention of PEP after ERCP mainly include somatostatin, nitroglycerin, non-steroidal anti-inflammatory drugs, enzyme inhibitors *etc*.

Octreotide is a synthetic somatostatin derivative, which acts similarly to somatostatin with respect to effectively inhibit the secretion of gastric acid and pancreatic enzymes. It reduces gastrointestinal motility and inhibits gallbladder emptying, whereby indirectly decreasing the secretory function of pancreas to suppress the secretion of cholecystokinin and pancreatic enzymes. Additionally, octreotide is able to regulate the cytokine cascade reaction, reduce inflammation and protect pancreatic parenchymal cells by inducing apoptosis of pancreatic alveolar cells [26].

Some studies have reported that proton pump inhibitors can inhibit gastric acid secretion, increase the pH value in the stomach, reduce the secretion of pancreatic juice and pancreatic enzymes due to acid stimulation, and reduce the pancreatic self-digestion process in inhibiting gastric acid secretion, which can

TABLE 4. Incidence of postoperative PEP and hyperamylasemia in four groups of patients with different disease types (n, %).

Group	n	Choledocholithiasis		Cholangiocarcinoma		Pancreatic head carcinoma		Others	
		PEP	Hyperamylasemia	PEP	Hyperamylasemia	PEP	Hyperamylasemia	PEP	Hyperamylasemia
Control	80	12.07 (7/58)	29.31 (17/58)	12.50 (2/16)	37.50 (6/16)	16.67 (1/6)	50.00 (3/6)	- (0/0)	- (0/0)
Octreotide	80	7.69 (4/52)	11.54 (6/52)	7.14 (1/14)	14.29 (2/14)	10.00 (1/10)	10.00 (1/10)	25.00 (1/4)	25.00 (1/4)
PPI	80	8.93 (5/56)	16.07 (9/56)	5.56 (1/18)	5.56 (1/18)	50.00 (2/4)	25.00 (1/4)	0.00 (0/2)	0.00 (0/2)
Combination	80	2.00 (1/50)	6.00 (3/50)^{ac}	0.00 (0/12)	8.33 (1/12)	0.00 (0/12)	16.67 (2/12)	0.00 (0/6)	16.67 (1/6)
χ^2		3.875	10.379	1.773	7.257	7.010	3.816	-	-
p		0.275	0.016	0.621	0.064	0.072	0.282	-	-

Note: Compared with control group, $^{a}p < 0.05$; compared with octreotide group, $^{b}p < 0.05$; compared with PPI group, $^{c}p < 0.05$. PEP: post-ERCP acute pancreatitis. PPI: proton pump inhibitor.

be used to prevent PEP [27, 28].

In this study, hemodiastase levels at different time points after procedure were significantly decreased in the octreotide group, PPI group and combined treatment group compared with the control group without preoperative pharmacological intervention. There was no significant difference in the incidence of PEP in patients using octreotide or PPI alone compared with the control group ($p > 0.05$), which may be related to factors such as the small sample size of the study and the small dose of the drug used. In addition, most studies have also shown that octreotide alone is ineffective in the prevention of PEP [29]. However, Li ZS *et al*. [30] showed that octreotide at a dosage $\geq$0.5 mg was effective in preventing PEP after ERCP and this result is different from the conclusion from clinical trials in Europe and the United States, which may be related to factors such as baseline information of the study population and differences in the pharmacological effects of octreotide between races.

Several drug combinations have been studied for their potential to reduce the risk of PEP, with the most research focusing on the use of octreotide in conjunction with PPI. In this study, we found that the incidence of postoperative PEP was significantly lower in the combine of octreotide and PPI than in the control group. In addition, the incidence of hyperamylasemia was reduced in the two drug pretreatment groups compared with control group. These results suggest that preadministration of octreotide or PPI alone is not effective in reducing postoperative PEP, but has good effect in preventing postoperative hyperamylasemia. The combination of the two drugs can effectively reduce the risk of postoperative PEP and hyperamylasemia. This may be related to the fact that their combination can play a complementary role to each other [31, 32].

For patients with different disease types, the incidence of postoperative hyperamylasemia was significantly changed in patients with choledocholithiasis after different preoperative medication interventions, as indicated by the lowest incidence of hyperamylasemia in patients who were given octreotide and PPI together, and it was significantly decreased compared with the remaining three groups. In contrast, the incidence of postoperative PEP and hyperamylasemia in patients with other disease types did not differ significantly after intervention with different drug regimens. This may be explained by the highest percentage of patients with choledocholithiasis in this study and the small size of cases in other disease types. To enhance the reliability of the study findings, the sample size will be increased in future study.

5. Conclusions

Taken together, preoperative application of octreotide or PPI alone acts similarly in the prevention of PEP and hyperamylasemia after ERCP, and their combination works better in preventing PEP.

AVAILABILITY OF DATA AND MATERIALS

The authors declare that all data supporting the findings of this study are available within the paper and any raw data can be obtained from the corresponding author upon request.

AUTHOR CONTRIBUTIONS

YZH—designed the study, carried them out, prepared the manuscript for publication and reviewed the draft of the manuscript; YZH, XLC and HL—supervised the data collection, analyzed the data, interpreted the data. All authors have read and approved the manuscript.

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

Ethical approval was obtained from the Ethics Committee of the Fifth Affiliated Hospital Sun Yat-sen University (Ethics Approval number: 201806477). Written informed consent was obtained from a legally authorized representative(s) for anonymized patient information to be published in this article.

ACKNOWLEDGMENT

Not applicable.

FUNDING

This research received no external funding.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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How to cite this article: Hao Liu, Xiaoling Chen, Yanzhi Han. Comparison of octreotide and proton pump inhibitor in the prevention of acute pancreatitis after endoscopic retrograde cholangiopancreatography for different diseases. Signa Vitae. 2023; 19(5): 238-243. doi: 10.22514/sv.2023.090.