Preventive and therapeutic significance of octreotide combined with lansoprazole on post-ERCP pancreatitis and its effect on serum amylase, inflammatory factors and immune function

ZHILIANG CHEN[1], HONG FU[1], JIANFENG FANG[1], JIANHUI YANG[1],
XIN ZHU[1], BINGXIANG CHENG[1] and TIANNV DING[2]

[1]Department of Hepatobiliary Surgery and [2]Endoscopy Center, Shaoxing People's Hospital
(Shaoxing Hospital, Zhejiang University School of Medicine), Shaoxing, Zhejiang 312000, P.R. China

Abstract. The study aimed to investigate the preventive and therapeutic significance of octreotide combined with lansoprazole on post-endoscopic retrograde cholangiopancreatography (ERCP) pancreatitis (PEP) and its effects on serum amylase (AMS), inflammatory factors and immune function. A total of 132 patients who underwent ERCP in Shaoxing People's Hospital (Shaoxing, China) were enrolled in the study and allocated into two groups: The study group (octreotide plus lansoprazole, 68 cases) and the control group (octreotide alone, 64 cases). The incidence of PEP and post-ERCP hyperamylasemia (PEH), the concentrations of serum AMS, interleukin-17 (IL-17) and tumor necrosis factor-α (TNF-α), as well as the T-lymphocyte population in peripheral blood were detected. The AMS levels in the study group were significantly lower than those in the control group at 6 and 24 h after treatment (P<0.001). The incidence of PEP and PEH, symptom disappearance time and hospital stay in the study group were significantly lower than those in the control group after treatment (P<0.05). The levels of IL-17 and TNF-α in the study group were significantly lower than those in the control group after treatment (all P<0.05). The percentage of CD3$^+$, CD4$^+$, CD8$^+$ cells and the ratio of CD4$^+$/CD8$^+$ in the study group were significantly higher than those in the control group after treatment (all P<0.05). The results indicated that octreotide combined with lansoprazole reduces AMS levels and the incidence of PEP, alleviates inflammation and improves the immune function.

Correspondence to: Dr Hong Fu, Department of Hepatobiliary Surgery, Shaoxing People's Hospital (Shaoxing Hospital, Zhejiang University School of Medicine), 568 Zhongxin Bei Road, Yuecheng, Shaoxing, Zhejiang 312000, P.R. China
E-mail: frx2lr@163.com; zjufh@163.com

Introduction

Endoscopic retrograde cholangiopancreatography (ERCP) is one of the most important methods for clinical diagnosis and treatment of biliary and pancreatic diseases (1). ERCP assists in the implementation of surgeries and the ERCP indications are increasing (2). However, it is a traumatic and invasive examination that may cause pancreatitis, hyperamylasemia, hemorrhage, perforation and other complications. Among them, post-ERCP pancreatitis (PEP) is the most common one, with an incidence rate of 7.7-10% (3-5). PEP patients without timely treatment are prone to develop severe acute pancreatitis, which may even lead to death in severe cases (6). Therefore, avoiding its occurrence is of great significance.

Clinically, conventional drugs for the prevention and treatment of PEP and post-ERCP hyperamylasemia (PEH) include somatostatin analogs and calcium channel blockers (7,8). Octreotide is a kind of synthetic somatostatin analogue that inhibits the secretion of pituitary, pancreas and gastrointestinal hormones (9). Although some progress has been made in the prevention of PEP by octreotide, the effect of the monotherapy is still unsatisfactory (10). As a new proton pump inhibitor (PPI), lansoprazole is effective in treating the gastroesophageal reflux disease and peptic ulcer (11); however, its effect on the prevention and treatment of PEP has hardly been investigated. In addition, inflammatory factors, such as interleukin-17 (IL-17) and tumor necrosis factor-α (TNF-α), increase gradually in the early stages of pancreatitis. TNF-α activates the lysozyme system, thus damaging pancreatic cells and participating in the progression of pancreatitis (12,13). Moreover, surgical trauma and anesthesia may cause disorders of the immune function, and low immune function is closely related to the development of pancreatitis (14).

Up to our knowledge, only a few previous studies have been reported on the preventive and therapeutic effects of octreotide combined with lansoprazole on PEP. Therefore, in the present study, the combination therapy was used to treat patients undergoing ERCP in order to explore its effects on PEP, serum amylase (AMS), inflammatory factors and immune function.

Patients and methods

General data. In this observational study, a total of 132 patients who underwent ERCP in Shaoxing People's Hospital (Shaoxing, China) from March, 2012 to June, 2015 were enrolled and allocated into two groups: The study group (treated with octreotide plus lansoprazole, 68 cases) and the control group (treated with octreotide alone, 64 cases). In the study group, there were 37 male and 31 female patients, aged 24-75 years with an average age of 59.4±10.1 years. In the control group, there were 36 male and 28 female patients, aged 22-74 years with an average age of 58.1±9.8 years. The study was approved by the Ethics Committee of Shaoxing People's Hospital (1536-40-16). Signed written informed consents were obtained from the patients and/or guardians.

Inclusion and exclusion criteria. Inclusion criteria: Patients who met the ERCP indications and the study followed the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) Statement guidelines; patients with complete clinical data, and aged 22-75 years. Exclusion criteria: Patients with surgical and anesthetic intolerance, or contraindications to drugs applied in this treatment; patients with previous hyperamylasemia or pancreatitis; patients receiving anti-inflammatory, immunosuppressive and non-steroidal anti-infection drugs in the past month; patients with abnormal coagulation function; patients with cognitive dysfunction and mental diseases; patients complicated with digestive tract ulcer, heart failure, respiratory failure, malignant tumor, hemorrhage, perforation, severe cardiovascular and cerebrovascular diseases, autoimmune diseases, connective tissue diseases, or liver and kidney dysfunctions.

Treatment methods. All patients received routine intramuscular injection of 10 mg of scopolamine (H41021048; Zhengzhou Suicheng Pharmaceutical Co., Ltd.), 50 mg of pethidine (H63020021; Qinghai Pharmaceutical Co., Ltd.), 10 mg of diazepam (H31021864; Shanghai Xudong Haipu Pharmaceutical Co., Ltd.) and 50 mg of propofol (H20030115; Sichuan Guorui Pharmaceutical Co., Ltd.) before ERCP for intravenous anesthesia. Oxygen inhalation, oxygen saturation and electrocardiogram monitoring were also performed. The ERCP was conducted by physicians in accordance with the standard manual. After ERCP, rehydration, anti-infection, anti-inflammatory and other supportive treatments were given. A total of 0.1 mg of octreotide (H120150364; Swiss Novartis Pharma Stein AG) was administered subcutaneously 1 h after ERCP, followed by 0.1 mg every 8 h for 3 times. On this basis, the patients in the study group were given intravenous drip of 30 mg of lansoprazole (H20100055; Shandong Luoxin Pharmaceutical Co., Ltd.) and 0.9% normal saline (100 ml) 1 h after ERCP, twice per day. The drip was completed within 30 min and the treatment was carried out for 7 consecutive days.

Evaluation indices. The incidence rates of PEP and PEH in the two groups were recorded. According to the diagnostic criteria of Ilone and Fauzi (15), patients with abdominal pain and tenderness at 2 h after ERCP, AMS levels >3 times higher than the normal upper limit, typical pancreatitis-like abdominal pain over 24 h and severe pain requiring hospitalization were diagnosed with PEP. PEH was diagnosed in patients whose serum AMS levels exceeded the normal value without the above clinical signs. The symptom disappearance time and hospital stay in the two groups were recorded.

Outcome measures. A total of 3 ml of venous blood were drawn before treatment, and at 6 and 24 h after treatment, respectively, and placed in vacuum tubes without anticoagulant. Additional 3-ml samples were collected 24 h after treatment and placed in a vacuum tube containing EDTA.

DxC 600 automatic biochemical analyzer (Beckman Coulter, Inc.) was used to detect AMS (702; Beijing Bioassay Technology Laboratory) levels before treatment, and at 6 and 24 h after treatment.

The levels of serum IL-17 and TNF-α in the two groups, before treatment and at 24 h after treatment, were measured by ELISA (kits purchased from Shanghai Xinfan Biotechnology Co., Ltd.; XF-HUMAN-0979 and XF-HUMAN-1140) (16). A standard well, a testing well and a blank control well (with no sample and ELISA kit) were set up. A 2-fold diluted standard (50 μl) was added into the standard well and 50 μl of sample were added into the testing well. After the addition of 50 μl of diluted antibody to each well, the plate was sealed and incubated for 2 h. Next, the liquid in each well was discarded, the well was repeatedly washed for 6 times and dried. A total of 100 μl of diluted horseradish peroxidase-labeled streptavidin were added to each well and the plate was incubated for 45 min. The liquid in each well was then discarded, the well was repeatedly washed for 6 times and dried. Afterwards, 100 μl of chromogenic substrate TMB solution were added to each well and incubated in the dark for 5 min. Finally, 100 μl of stop solution were added. The optical density was measured at a wavelength of 450 nm using Multiskan MK3 microplate reader (Shanghai Thermo Fisher Scientific, Inc.) and the IL-17 and TNF-α levels were measured.

FACSCanto flow cytometer (BD Biosciences) was employed to detect the T-lymphocyte population in peripheral blood before treatment and at 24 h after treatment. A total of 20 μl from 1 ml of EDTA-treated peripheral venous blood was added into an Tru COUNT tube containing known quantities of freeze-dried standard fluorescent microspheres. The mixture was incubated with mouse anti-human monoclonal antibodies conjugated with fluorescein isothiocyanate (FITC) or phycoerythrin (PE): Anti-CD3-PE, anti-CD4-FITC, anti-CD8-PE (Shanghai Hengfei Biological Technology Co., Ltd.; cat. nos. 130-103-130, 130-109-536, 130-098-078, 5 μl each) in the dark at room temperature for 15 min. Following a reaction with red blood cell lysate (450 μl) for 15 min, a flow cytometer was used to measure the sample and CELLQUEST software (Becton-Dickinson) was used to analyze the percentages of $CD3^+$, $CD4^+$ and $CD8^+$ cells.

Statistical analysis. SPSS 22.0 software (Guangzhou Coslan Instrument Co., Ltd.) was used for the statistical analysis of the data. Measurement data were expressed as the mean ± standard deviation (mean ± SD), and the intergroup comparison was conducted by independent samples t-test, whereas the intragroup comparison was conducted by paired t-test. Count data were expressed by the number of cases and percentage [n (%)] and the intergroup comparison between groups was

Table I. Patient general data in the study and control groups [n (%), mean ± SD].

Characteristics	Study group (n=68)	Control group (n=64)	t/χ^2 value	P-value
Sex			0.045	0.832
Male	37 (54.41)	36 (56.25)		
Female	31 (45.59)	28 (43.75)		
Age (years)	59.4±10.1	58.1±9.8	0.750	0.455
BMI (kg/m^2)	23.57±3.48	23.78±3.22	0.359	0.720
Disease type			0.870	0.351
Choledocholithiasis	46 (67.65)	48 (75.00)		
Obstructive jaundice	22 (32.35)	16 (25.00)		
ERCP duration (min)	31.12±8.13	30.27±8.15	0.600	0.550
Hypertension			0.005	0.945
Yes	3 (4.41)	2 (3.12)		
No	65 (95.59)	62 (96.88)		
Diabetes			0.244	0.621
Yes	2 (2.94)	4 (6.25)		
No	66 (97.06)	60 (93.75)		
Duodenal diverticulum			0.495	0.482
Yes	15 (22.06)	11 (17.19)		
No	53 (77.94)	53 (82.81)		
Smoking history			0.238	0.625
Yes	29 (42.65)	30 (46.88)		
No	39 (57.35)	34 (53.12)		
Drinking history			0.535	0.465
Yes	35 (51.47)	37 (57.81)		
No	33 (48.53)	27 (42.19)		
Balloon dilation			1.072	0.300
Dilated	40 (58.82)	45 (70.31)		
Undilated	28 (41.18)	19 (29.69)		
White blood cells (x10^9/l)	6.07±2.02	5.86±1.72	0.641	0.523
Platelets (x10^9/l)	153.46±32.69	162.58±35.51	1.536	0.127
Residence			0.189	0.664
Urban	46 (67.65)	41 (64.06)		
Rural	22 (32.35)	23 (35.94)		

BMI, body mass index; ERCP, endoscopic retrograde cholangiopancreatography.

conducted by Chi-square test. The data of multiple time points were analyzed by repeated measures analysis of variance, and LSD-t-test was the post-hoc text used for pairwise comparisons. P<0.05 was considered to indicate a statistically significant difference.

Results

Patient general data in the two groups. There was no significant difference in sex, age, body mass index (BMI), disease type, ERCP duration, hypertension, diabetes, duodenal diverticulum, smoking history, drinking history, balloon dilatation, white blood cells, platelets and residence between the two groups (P>0.05; Table I).

Serum AMS levels in the two groups at different time points. In the study group, the serum AMS levels before treatment,

at 6 and 24 h after treatment were 59.24±17.02, 104.32±20.31 and 97.12±14.32 U/l, respectively, whereas those in the control group were 58.74±15.32, 183.65±17.43 and 166.32±21.53 U/l, respectively. Thus, the serum AMS levels in the two groups at 6 h after treatment were significantly higher than those before treatment (P<0.001). The levels decreased significantly at 24 h after treatment compared with those at 6 h after treatment (P<0.001); however, they remained higher than those before treatment (P<0.001). There was no significant difference in serum AMS levels between the study and the control group before treatment (P>0.05). AMS expression in the study group was significantly lower than that in the control group at 6 and 24 h after treatment (P<0.001). Data are shown in Fig. 1.

Incidence of PEP and PEH in the two groups. In the study group, PEP occurred in 1 case (1.47%) and PEH occurred

Table II. Comparison of incidence of pancreatitis and hyper-amylasemia between the two groups [n (%)].

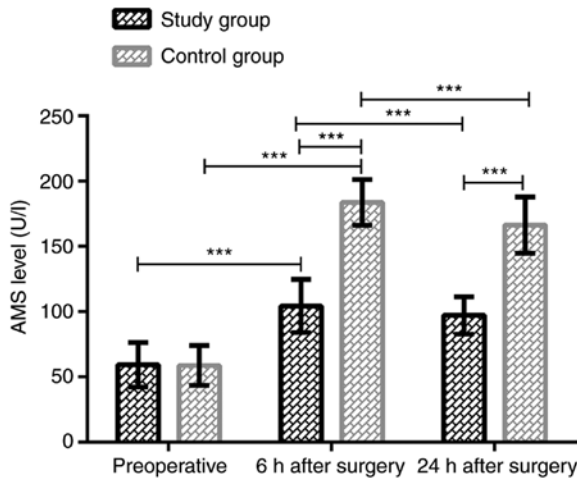| Group	n	Pancreatitis	Hyperamylasemia
Study group	68	1 (1.47)	12 (17.65)
Control group	64	6 (9.38)	23 (35.94)
χ^2 value	-	2.338	5.661
P-value	-	0.021	0.017

Figure 1. Comparison of serum AMS levels between the study and the control group at different time points. The serum AMS levels in the two groups at 6 h after treatment were significantly higher than those before treatment (P<0.001). At 24 h after treatment, the AMS levels decreased significantly compared with those at 6 h after treatment (P<0.001); however, they remained higher than those before treatment (P<0.001). There was no significant difference in serum AMS levels between the study and the control group before treatment (P>0.05). AMS levels were significantly lower in the study group than those in the control group at 6 and 24 h after treatment (P<0.001). ***P<0.001. AMS, amylase.

in 12 cases (17.65%). In the control group, PEP occurred in 6 cases (9.38%) and PEH in 23 cases (35.94%). The incidence of postoperative PEP and PEH in the study group was significantly lower than that in the control group (P<0.05). Data are presented in Table II.

Serum IL-17 levels in the two groups before and after treatment. The serum IL-17 levels in the study group before and at 24 h after treatment were 6.62±2.31 and 7.51±2.04 pg/ml, respectively. In the control group, IL-17 levels were 6.45±2.58 and 9.04±2.75 pg/ml, respectively. There was no significant difference in serum IL-17 levels between the two groups before treatment (P>0.05). At 24 h after treatment, the IL-17 expression was significantly increased in both groups (P<0.05), and in the study group, IL-17 expression was significantly lower than that in the control group (P<0.001). Data are shown in Fig. 2.

Serum TNF-α levels in the two groups before and after treatment. The serum TNF-α levels in the study group were 74.35±25.72 pg/ml before treatment and 82.29±17.18 pg/ml at 24 h after treatment, whereas in the control group were
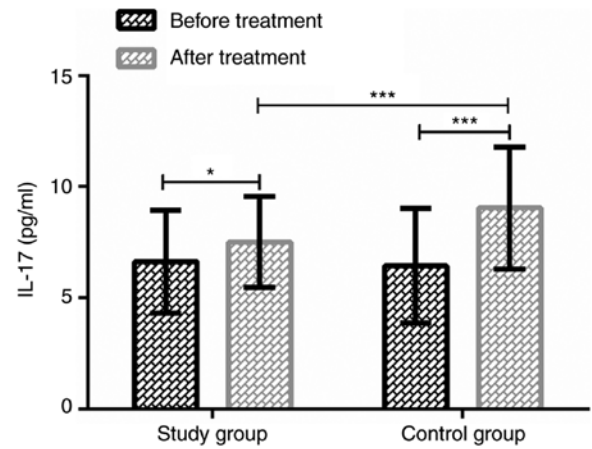

Figure 2. Comparison of serum IL-17 levels between the two groups before and after treatment. There was no significant difference in serum IL-17 levels between the two groups before treatment (P>0.05). At 24 h after treatment, the levels in the two groups were significantly increased (P<0.05), and IL-17 expression in the study group was significantly lower than that in the control group (P<0.001). *P<0.05, ***P<0.001. IL-17, interleukin-17.

76.13±18.91 and 89.73±24.32 pg/ml, respectively. There was no significant difference in serum TNF-α levels between the two groups before treatment (P>0.05). After treatment, the TNF-α expression was significantly increased in both groups (P<0.05), and in the study group, TNF-α expression was significantly lower than that in the control group (P<0.05). Data are shown in Fig. 3.

T-lymphocyte population in the two groups before and after treatment. There was no significant difference in the percentages of CD3+, CD4+ and CD8+ cells and the CD4+/CD8+ ratio in peripheral blood between the two groups before treatment (P>0.05). At 24 h after treatment, the values of CD3+, CD4+, CD8+ and CD4+/CD8+ in both groups were significantly decreased (P<0.05), and in the study group were significantly higher than those in the control group (P<0.05) (Table III and Fig. 4).

Symptom disappearance time and hospital stay in the two groups. The symptom disappearance time and hospital stay in the study group were significantly lower than those in the control group (P<0.001) (Table IV).

Discussion

ERCP is an important method for the treatment of biliary and pancreatic diseases that not only cures the disease, but also relieves the pain of patients caused by surgical trauma to the greatest extent (17). However, even with the continuous development of ERCP technology, patients still suffer from PEP, PEH and other complications (18).

Previous studies on octreotide in the prevention of PEP are numerous. For example, Thomopoulos *et al* (19) have pointed out that octreotide may reduce the incidence of PEP. Moreover, in a multi-center randomized controlled trial by Bai *et al* (20), prophylactic use of somatostatin (octreotide) was shown to decrease the incidence of PEP. However, Binmoeller *et al* (21) showed that octreotide may have no

Table III. Comparison of T-lymphocyte populations in peripheral blood between the two groups (mean ± SD).

Group	Study group (n=68)	Control group (n=64)	t value	P-value
CD3$^+$ (%)				
Before treatment	63.13±4.65	63.07±4.75	0.073	0.942
After treatment (24 h)	57.76±4.66	54.65±4.82	3.769	<0.001
t value	6.727	9.954	-	-
P-value	<0.001	<0.001	-	-
CD4$^+$ (%)				
Before treatment	36.53±4.42	35.67±4.31	1.131	0.260
After treatment (24 h)	34.02±4.15	31.16±4.23	3.920	<0.001
t value	3.414	5.975	-	-
P-value	<0.001	<0.001	-	-
CD8$^+$ (%)				
Before treatment	25.61±3.32	26.39±3.15	1.383	0.168
After treatment (24 h)	24.37±3.17	23.16±3.08	2.222	0.028
t value	2.228	5.951	-	-
P-value	0.028	<0.001	-	-
CD4$^+$/CD8$^+$				
Before treatment	1.51±0.23	1.45±0.23	1.498	0.137
After treatment (24 h)	1.34±0.18	1.25±0.28	2.210	0.029
t value	4.800	4.416	-	-
P-value	<0.001	<0.001	-	-

Table IV. Symptom disappearance time and hospital stay in the two groups (mean ± SD).

Group	n	Symptom disappearance time (days)	Hospital stay (days)
Study group	68	1.6±1.3	12.7±1.2
Control group	64	3.5±3.2	14.6±1.4
t value	-	4.517	8.387
P-value	-	<0.001	<0.001

Figure 3. Comparison of serum TNF-α levels between the two groups before and after treatment. There was no significant difference in serum TNF-α levels between the two groups before treatment (P>0.05). At 24 h after treatment, the levels in the two groups were significantly increased (P<0.05), and TNF-α expression in the study group was significantly lower than that in the control group (P<0.05). *P<0.05, ***P<0.001. TNF-α, tumor necrosis factor-α.

preventive effect on PEP. The development of PEP is closely related to the increase of gastric acid. Abnormally increased gastric acid enters the inner wall of small intestine and duodenum, resulting in high pressure in pancreatic duct, leading to edema and necrosis of pancreas (22). Therefore, inhibiting gastric acid secretion may also be the key to prevent PEP (23). Lansoprazole is a PPI, another clinical drug to prevent PEP, that is widely used in the treatment of peptic ulcer and other acid-related gastrointestinal diseases by reducing gastric acid secretion (24). Up to our knowledge, there has been no previous report on the prevention and treatment of PEP by octreotide combined with lansoprazole. The results of the present study revealed that the AMS levels in the study group were significantly lower than those in the control group at 6 and 24 h after ERCP, and the incidence of PEP and PEH, symptom disappearance time and hospital stay in the study group were significantly lower than those in the control group. These indicate that octreotide
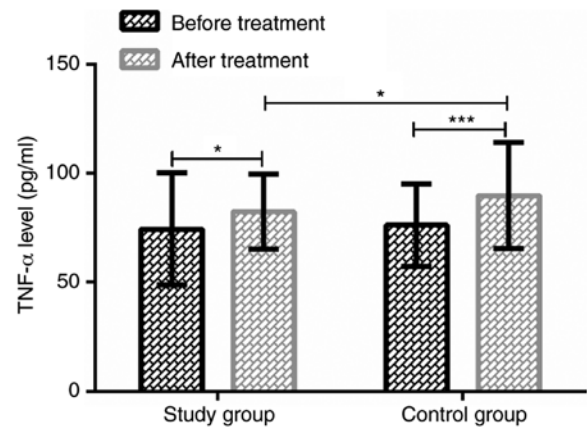
combined with lansoprazole reduces AMS levels and the incidence of PEP, and accelerates patient recovery. The study of Yoo et al (25) showed that PPIs have no effect on the clinical progress of acute pancreatitis. In addition, in the study of Alhazzani et al (26), PPIs and histamine 2 receptor antagonists were reported to prevent stress ulcer in critically ill patients. This suggests that lansoprazole inhibits gastric acid secretion, leading to the reduction of pancreatin and pancreatic secretion (27), thus decreasing the incidence of PEP. Therefore, octreotide combined with lansoprazole plays a preventive role in PEP.
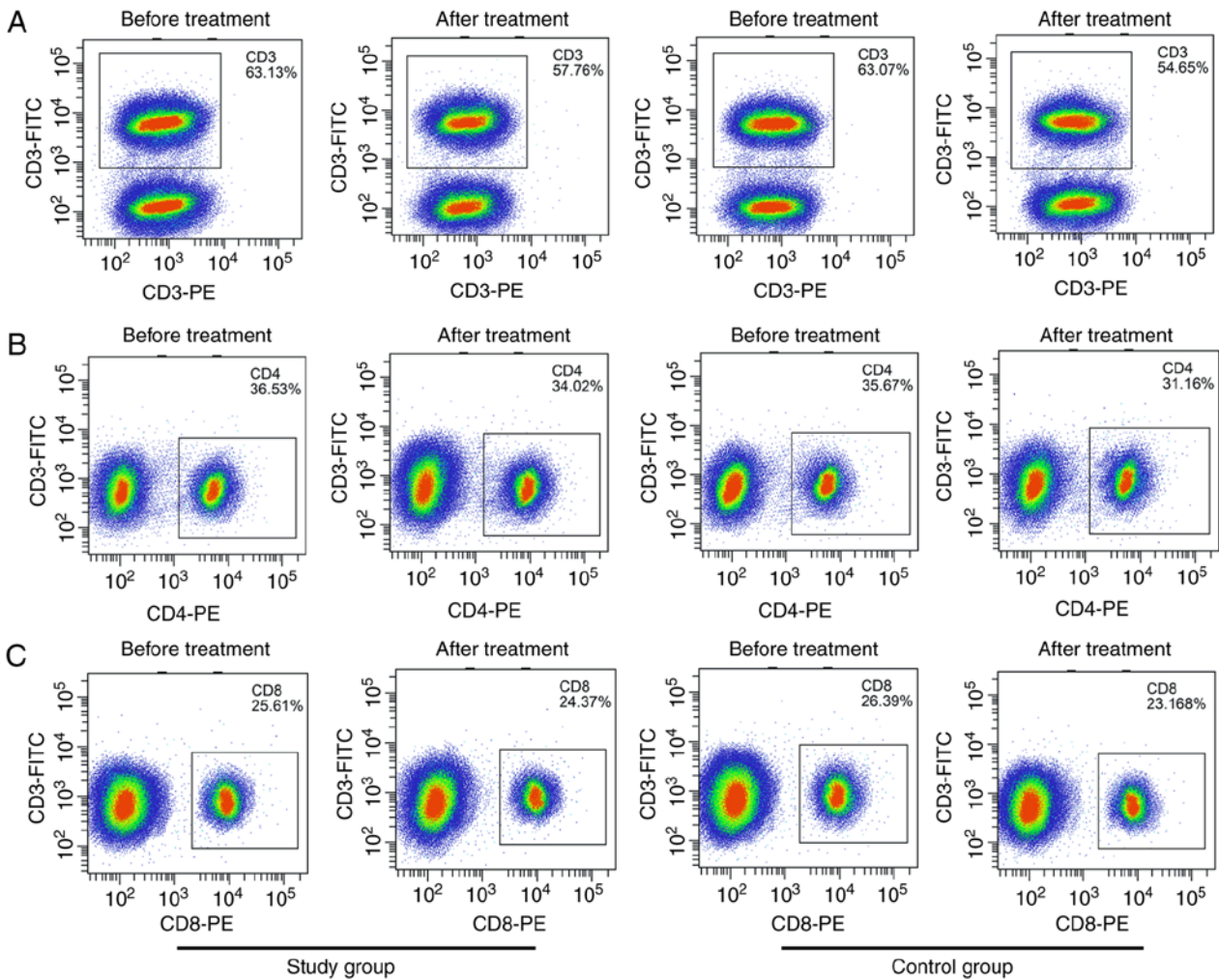
Figure 4. T-lymphocyte subsets in peripheral blood before and after treatment. The dot plots of (A) CD3+ (B) CD4+ and (C) CD8+ before and at 24 h after treatment in the two groups are presented.

The release and activation of inflammatory cytokines are not only a significant cause of pancreatitis, but also an important factor of pancreatic tissue necrosis and organ dysfunction (28). Pancreatitis increases the release of some inflammatory cytokines and leads to the over-release of IL-17, TNF-α and other pro-inflammatory cytokines (29). Previous studies have shown that IL-17 and TNF-α are overexpressed in the early stages of pancreatitis, and their levels are closely related to the severity of the disease (27,30). In the present study, the levels of serum IL-17 and TNF-α in the study and the control groups after treatment were significantly higher than those before treatment, and the levels in the study group were significantly lower than those in the control group after treatment. These results indicate that inhibition of inflammatory cytokines may be one of the mechanisms of octreotide combined with lansoprazole in preventing and treating PEP. In the study of Wang *et al* (31), the levels of AMS and inflammatory cytokines TNF-α, IL-6 and IL-8 in serum were significantly increased after ERCP. However, compared with octreotide monotherapy, the above levels in patients treated with octreotide combined with indomethacin were significantly decreased. Hackert *et al* (32) revealed that PPIs are anti-inflammatory and can reduce the progression of pancreatitis, inflammation and the expression of adhesion proteins. Therefore, inhibition of inflammatory factors may be one of its therapeutic mechanisms.

Moreover, there is an imbalance in the immune function of patients with pancreatitis, and the disorder of immune function can further induce macrophage activation and pro-inflammatory response in the early stage of pancreatitis (33). T-lymphocyte subsets are vital effector cells reflecting the immune function of the body and changes in their percentages often reflect changes in the immune function of the patients (34). T-lymphocyte subsets are separated into CD3+, CD4+ and CD8+ cells according to the difference of surface CD molecules. In the present study, the percentages of CD3+, CD4+, CD8+ cells and the CD4+/CD8+ ratio in the two groups after treatment were significantly lower than those before treatment, and in the study group were significantly higher than those in the control group. These results suggest that octreotide combined with lansoprazole improved the disordered immune function induced by ERCP. Vaidya *et al* (35) reported that octreotide has no effect on T-lymphocyte subsets in patients with thyroid-associated ophthalmopathy, whereas the research of Larussa *et al* (36) confirmed that lansoprazole regulates Th1/Th2 immune response of human gastric mucosa, thus improving the clinical symptoms of gastritis patients. Because lansoprazole

inhibits inflammatory cytokines and reduces their release, it has a protective effect on the immune function. However, the mechanism need to be further investigated.

The present study confirmed that octreotide combined with lansoprazole has preventive and therapeutic effects on PEP and can improve the inflammatory factors and immune function of patients. However, there are still several limitations. For example, no randomized control trials were performed, leading to biases in our results. Besides, only changes in IL-17 and TNF-α were measured. In addition, lansoprazole has been reported to induce side effects, such as hypomagnesemia (37), which was not mentioned in our study. These limitations will be addressed in future studies to corroborate the conclusions of the present study.

In conclusion, octreotide combined with lansoprazole reduces serum AMS levels and the incidence of PEP, and also alleviates inflammation while improving the patients' immune function.

Acknowledgements

Not applicable.

Funding

Availability of data and materials

The datasets used and/or analyzed during the present study are available from the corresponding author on reasonable request.

Authors' contributions

ZC, HF, JF and JY conceived and designed the study. ZC, XZ, BC and TD were responsible for the data acquisition and analysis. HF, JF and XZ were responsible for the interpretation of the data and the drafting of the manuscript. ZC and HF revised the manuscript critically for important intellectual content. All authors read and approved the final version of the manuscript.

Ethics approval and consent to participate

The study was approved by the Ethics Committee of Shaoxing People's Hospital (Shaoxing, China) (1536-40-16). Signed written informed consents were obtained from the patients and/or guardians.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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