



Comparison of intraoperative conditions and postoperative inflammatory response and immune response between patients with common bile duct stones undergoing ESD and EST

Kun Zhu , Jian-Ping Wang, Jin-Gen Su

General Surgery Department, Shanghai Jiading Central Hospital, Jiading District, Shanghai 201800, China

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ABSTRACT

Objective: To analyze the differences in intraoperative conditions and postoperative inflammatory response and immune response levels in patients with common bile duct stones undergoing ESD and EST treatment. **Methods:** A total of 565 patients with common bile duct stones who underwent ERCP treatment in our hospital from January 2013 to December 2015 were included in the study, patients' treatment and testing results were analyzed retrospectively, and then patients were divided into the observation group 300 cases that received ESD treatment and control group 265 cases that received EST treatment. Differences in intraoperative stress levels as well as postoperative inflammation, nutrition-related index and immune response levels were compared between two groups. **Results:** Intraoperative N, Cor, C-P and NK cell levels of observation group were lower than those of control group, and FT3 level was higher than that of control group; postoperative inflammation-related factors such as IL-6, CRP, PCT, CA19-9 and CEA levels were lower than those of control group, protein nutrition indexes such as TP, Alb, PA, TRF and RBP values were higher than those of control group, and immune indexes such as CD4+, CD4+/CD8+, IgA, IgM and IgG levels were higher than those of control group while CD8+ level was lower than that of control group. **Conclusion:** ESD for the treatment of patients with common bile duct stones is better than EST treatment in reducing surgical stress, optimizing postoperative physical status and other aspects.

1. Introduction

Common bile duct stones belong to common clinical biliary tract disease, and endoscopic removal of stones is currently the most applied efficient and less traumatic treatment. Endoscopic sphincterotomy (EST) has been widely used in clinical practice, but for patients with larger stones or more complications, EST success rate greatly reduces[1–2]. Endoscopic sphincterotomy combined with balloon dilatation (ESD) separates the pancreatic duct opening and bile duct opening, and guides the balloon to dilate in bile duct sphincter direction, it reduces pancreatic duct sphincter levels and risk of postoperative pancreatitis on the premise

of ensuring the stone removal, and it is the latest treatment of common bile duct calculi with both efficiency and safety[3]. In the study, the differences in intraoperative conditions and postoperative inflammatory response and immune response levels in patients with common bile duct stones undergoing ESD and EST treatment were mainly analyzed, hereby reported as follows.

2. Research subjects

2.1. Inclusion and exclusion criteria

A total of 565 patients with common bile duct stones who underwent ERCP treatment in our hospital from January 2013 to December 2015 were the research subjects. Inclusion criteria: 1) with confirmed diagnostic criteria for common bile duct stones

Corresponding author: Kun Zhu, General Surgery Department, Shanghai Jiading Central Hospital, Jiading District, Shanghai 201800, China.

Tel: 67073028; 18960862999.

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through abdominal B ultrasound and MRI scanning; 2) diagnosed for the first time and without systematic treatment; 3) conforming to the indications of endoscopic treatment; 4) patients and families learned about the research process and then signed the informed consent. Exclusion criteria: 1) pregnant or breastfeeding women; 2) those with severe heart, liver, kidney and other viscera dysfunction; 3) those with malignant tumor or diseases of the immune system; 4) those with obviously abnormal coagulant function; 5) those associated with mental illness and couldn't cooperate with treatment.

2.2. Grouping and general information

Patients' treatment and testing results were analyzed retrospectively, and then patients were divided into the observation group 300 cases receiving ESBD treatment and control group 265 cases receiving EST treatment. Observation group included 156 male cases and 144 female cases, they were 36-72 years old and the average was (49.56 ± 8.78) years; control group included 135 male cases and 130 female cases, they were 35-69 years old and the average was (48.97 ± 8.99) years. Differences in baseline information of two groups were not statistically significant, $P > 0.05$ and they were comparable.

2.3. Methods

2.3.1 Treatment methods

Both groups of patients received preoperative subcutaneous injection of octreotide 0.1 mg, once every 6 h, and received intravenous injection of pethidine 50 mg before the operation, and ECG monitoring was adopted in the process of specific operation.

Control group received endoscopic sphincterotomy (EST) treatment, specifically as follows: stones were found through common bile duct development, duodenal papilla was incised in 12 o'clock direction, and the incision length should not exceed papilla-side uplifted root. In cases of ampulla impacted stone or intubation difficulties, needle-knife fistulosphincterotomy was performed, stones with smaller diameter were removed with the basket, and stones with larger diameter were crushed with lithotripter at first. After the stones were removed, balloon catheter was used to clean common bile duct, and balloon angiography was performed at last to confirm complete stone removal.

Observation group received endoscopic sphincterotomy combined with balloon dilation (ESBD) treatment, specifically as follows: the guide wire was inserted into bile ducts, a small slicer was placed along the guidewire, mixed 25-30 W current was used to incise the uplifted part of papilla (length was within 1/3 of the uplifted area). Appropriate balloon was chosen according to the stone size and inferior bile common duct diameter, placed in bile duct, continuously expanded for 1-2 min and then taken out, it was expanded again after

30 s if the expansion effect was not satisfactory, and finally basket was used to remove the stones.

2.3.2 Assessment means

2.3.2.1 Intraoperative stress-related indexes

10 min before the end of operation, peripheral venous blood was extracted and centrifuged to get supernatant and detect adrenaline (N), cortisol (Cor), C-peptide (C-P), free triiodothyronine (FT3) and NK cells in it.

2.3.2.2 Inflammation

2 mL peripheral venous blood was extracted from patients 1d after operation, and enzyme-linked immunosorbent assay (ELISA) was used to determine the levels of inflammatory factors, including interleukin-6 (IL-6), C-reactive protein (CRP), procalcitonin (PCT) and carbohydrate antigen 19-9 (CA19-9) and carcinoembryonic antigen (CEA).

2.3.2.3 Serum protein nutrition indexes

2 mL peripheral venous blood was extracted from patients 1 d after operation as specimen and centrifuged to get serum, then the biuret method was used to determine total protein (TP) level, bromocresol green was used to determine albumin (Alb) levels, immunoturbidimetry was used to determine prealbumin (PA) levels, enzyme-linked immunosorbent assay (ELISA) was used to determine human transferrin (TRF) levels, and chemiluminescence was used to determine retinol binding protein (RBP) levels.

2.3.2.4 Immune function indexes

2 mL venous blood was extracted respectively before operation and 1 d after operation, anticoagulated with sodium citrate and then centrifuged to get supernatant, and ELISA method was used to determine immunoglobulin A (IgA), immunoglobulin M (IgM) and immunoglobulin G (IgG) levels; another 2 mL peripheral venous blood was taken to incubate different antibodies, and then flow cytometry was used to determine the proportion of CD4+ and CD8+.

2.4 Statistical methods

Data obtained in the study was analyzed by SPSS 23.0 software, measurement data comparison was by t test, count data comparison was by chi-square test and $P < 0.05$ was set as the standard of statistical significance in differences.

3. Results

3.1 Intraoperative stress-related indexes

Surgical trauma is the biggest cause of intraoperative stress, severe stress can even affect patients' postoperative rehabilitation, and so the stress index is one of the effective indicators to judge the trauma of different surgeries. In the study, intraoperative N, Cor, C-P and NK cell levels of observation group were lower than those of control group, and FT3 level was higher than that of control group ($P<0.05$), shown in Table 1.

3.2 Inflammation

Both common bile duct stones and surgical trauma can make patients in postoperative systemic inflammatory state, and severe cases further inhibit the body's immune function and delay the body rehabilitation. In the study, comparison of the levels of early postoperative inflammation-related factors between two groups showed that inflammation-related factors such as IL-6, CRP, PCT, CA19-9 and CEA levels of observation group 1d after operation were lower than those of control group ($P<0.05$), shown in Table 2.

3.3 Serum protein nutrition indexes

Table 1.

Comparison of intraoperative stress-related index values between two groups.

Groups	N (ng/mL)	Cor (nmol/L)	C-P (nmol/L)	FT3 (pmol/L)	NK cell (%)
Observation	135.38±15.83	205.37±25.47	0.95±0.08	5.19±0.63	24.17±2.04
Control	241.75±30.92	412.52±48.61	1.76±0.18	3.78±0.41	28.53±2.74
<i>t</i>	10.843	15.382	5.839	6.923	5.849
<i>P</i>	<0.05	<0.05	<0.05	<0.05	<0.05

Table 2.

Comparison of postoperative inflammatory response levels between two groups.

Groups	IL-6 (ng/L)	CRP (mg/L)	PCT (μg/L)	CA19-9(μmL)	CEA (μg/L)
Observation	17.38±2.41	41.73±5.06	5.12±0.68	18.44±2.04	2.84±0.35
Control	30.95±4.17	69.61±7.28	8.63±0.95	30.21±3.74	5.62±0.69
<i>t</i>	7.834	8.273	6.283	7.347	6.394
<i>P</i>	<0.05	<0.05	<0.05	<0.05	<0.05

Table 3.

Comparison of postoperative serum protein nutrition index values between two groups.

Groups	TP (g/L)	Alb (g/L)	PA (mg/L)	TRF (mg/L)	RBP (mg/L)
Observation	70.37±8.05	48.27±5.11	321.36±45.49	2.84±0.31	45.36±5.38
Control	61.26±6.84	39.51±4.03	233.49±34.77	1.76±0.21	30.75±3.95
<i>t</i>	6.382	7.392	12.374	5.392	7.392
<i>P</i>	<0.05	<0.05	<0.05	<0.05	<0.05

Table 4.

Comparison of cellular immunity levels between two groups before and after operation.

Groups	CD4+ (%)		CD8+ (%)		CD4+ / CD8+	
	Before operation	After operation	Before operation	After operation	Before operation	After operation
Observation	36.21±3.48	36.04±3.75	26.15±2.95	24.37±2.84	1.58±0.14	1.53±0.14
Control	36.17±3.95	34.76±3.41	26.74±2.78	26.16±3.02	1.57±0.18	1.42±0.16
<i>t</i>	0.217	5.283	0.229	5.893	0.243	7.432
<i>P</i>	>0.05	<0.05	>0.05	<0.05	>0.05	<0.05

Protein nutrition indicators are closely associated with the body's consumption state, and under excessive consumption state, protein loss increases and wound healing is difficult. In the study, early postoperative serum protein nutrition indexes such as TP, Alb, PA, TRF and RBP values of observation group were higher than those of control group ($P<0.05$), shown in Table 3.

3.4 Cellular and humoral immunity levels

The body's immune function is directly related to patients' conditions and surgical trauma, and will directly determine patients' treatment prognosis. In the study, comparison of perioperative immune function between two groups showed that differences in preoperative serum cellular and humoral immunity indexes of two groups were not statistically significant ($P>0.05$), and early postoperative serum CD4+, CD4+ / CD8+, IgA, IgM and IgG levels of observation group were higher than those of control group, and CD8+ level was lower than that of control group ($P<0.05$), shown in Table 4 and 5.

Table 5.

Comparison of serum immunoglobulin levels between two groups before and after operation (g/L).

Groups	IgA		IgM		IgG	
	Before operation	After operation	Before operation	After operation	Before operation	After operation
Observation	2.23±0.27	2.12±0.23	1.18±0.19	1.12±0.11	11.73±1.84	11.02±1.32
Control	2.29±0.23	1.94±0.21	1.15±0.18	0.91±0.09	11.59±1.75	7.86±0.85
<i>t</i>	0.217	5.283	0.229	5.893	0.243	7.432
<i>P</i>	>0.05	<0.05	>0.05	<0.05	>0.05	<0.05

4. Discussion

Common bile duct calculi belong to clinical common disease, the current incidence is about 5.6%, the proportion of late secondary to acute cholangitis is higher, and timely surgical removal of the stones in bile ducts is the most effective treatment method. The proportion of common bile duct stones in the middle-aged and elderly is above 15%, these patients are with lower basic immunity and mostly associated with hypertension, diabetes, coronary heart disease and other important viscera dysfunction, the traumatic shock from surgery can bring huge blow to patients and severe cases may have multiple organ failure and even death[4]. So for patients with common bile duct calculi, the surgical method with positive effect and small trauma should be chosen. Both endoscopic sphincterotomy combined with balloon dilation (ESBD) and endoscopic sphincterotomy (EST) are the classic methods of treatment of common bile duct stones, the implementation of the EST needs the coordination of appropriate papilla position and angle, ESBD can remove large bile duct stones, but it is less reported at home, and there is no clear judgment on the advantages and disadvantages of the clinical application of the two[5,6]. In the study, patients with common bile duct stones treated in our hospital were retrospectively analyzed and divided into patients who received ESBD or EST treatment according to surgical methods, and the values of a series of intraoperative and postoperative indexes were further analyzed in order to judge which surgery was more suitable for the treatment of common bile duct stones.

Stress is the protective response of the body on injury, excessive stress will suppress body's immune function, and severe cases affect patients' postoperative rehabilitation and even promote related complications. So stress is one of the main evaluation indexes of surgical efficacy, the levels of intraoperative stress-related indexes of two groups were monitored at first in the study, and results showed that serum N, Cor, C-P and NK cell levels of observation group were lower[7,8]. Studies have shown that cortisol (Cor), C-peptide (C-P) and free triiodothyronine (FT3) levels in patients will significantly increase under stress state, so the three can be used as the sensitive indexes of stress response, and compared with the serum glucose levels, they have higher accuracy. When the body is badly

stimulated, locus coeruleus-sympathetic-adrenal medulla axis is first excited, epinephrine is massively released, and the change of serum catecholamine level also becomes a sensitive indicator reflecting the body's stress response. NK cells belong to large granular cells, can directly kill effector target cells, and have antitumor, anti-infection, immunoregulation and other effect[9]. In cases of stress response such as trauma, the generation of inflammation-related cells can directly or indirectly restrain NK cell activity, and therefore, the determination of NK cell activity can intuitively reflect the body's stress response. Results of the study showed that the intraoperative stress extent was lighter in patients with common bile duct stones who received ESBD treatment, it didn't need to incise the duodenal papilla sphincter and it has advantages in reducing surgical trauma, postoperative hemorrhage risk and other aspects.

Common bile duct stones themselves can cause inflammation in bile duct and surgical trauma can also increase the secretion of inflammation-related factors. Interleukin-6 (IL-6) C-reactive protein (CRP) and procalcitonin (PCT) are the main cytokines of acute-phase tissue inflammation, and are mostly used for judgment of early postoperative inflammatory complications. More studies have confirmed that IL-6, PCT and CRP are positively correlated with the degree of inflammatory response and tissue damage[10]. IL-6 can promote precursor B-cell transformation into antibody-producing cell, and promote the release and function of adrenal cortical hormone; PCT can reflect the activity of systemic inflammation, and both infection and trauma can induce massive generation of PCT; CRP can activate the complement system, further release inflammatory mediators and promote cell adhesion and phagocytosis reaction[11,12]. Carbohydrate antigen 19-9 (CA19-9) and carcinoembryonic antigen (CEA) are the common tumor markers for clinical diagnosis of bile duct cancer, and it is clinically discovered that in cholangitis, obstructive biliary duct disease and other states, their levels can increase, and as the body's inflammatory state decreases, the levels of the two drop. So CA19-9 and CEA can also be used as the inflammatory markers of bile duct disease, and their expression levels are positively correlated with the degree of inflammation[13]. In the study, results showed that early postoperative serum inflammation-related factors such as IL-6, CRP, PCT, CA19-9 and CEA levels of observation group were lower, indicating that ESBD treatment could avoid the occurrence of excessive postoperative inflammatory state in patients and help the

disease rehabilitation.

In addition to intraoperative stress state, patients' postoperative nutrient immunity will also directly determine treatment prognosis. Related protein indexes in circulating blood can all reflect patients' state of nutrition, and in the study, early postoperative serum protein nutrition indexes such as TP, Alb, PA, TRF and RBP values of observation group were higher, indicating that patients' state of nutrition was better after ESD[14]. As for immune function, cellular and humoral immunity indexes such as CD4+, CD4+/CD8+, IgA, IgM and IgG levels in circulating blood of observation group 1d after operation were higher, indicating that ESD caused less immunosuppression to patients. ESD improves the operation of endoscopic papillary balloon dilation (EPBD), which separates the pancreatic duct opening and bile duct opening by means of duodenal papilla incision, and effectively guides the balloon dilation in the direction of bile duct sphincter without increasing trauma. Compared with EST, EPBD has significant advantages in effective stone removal (especially those with larger diameter), reducing pancreatic duct sphincter oppression, etc[15]. Serum protein nutrition indicators not just represent the overall nutritional status of the body, and because proteins are mainly synthesized by the liver, stone stimulation to the liver causes certain influence on digestion and absorption of protein substance by the liver, so the protein nutrition indicators can indirectly reflect the effect of stone treatment. Both surgical trauma and inflammatory stimulation can suppress immune function, the fluctuations of humoral immunity and cellular immunity index levels are directly influenced by surgical trauma and inflammation, and therefore, results in the study showed that after patients with common bile duct stones received ESD treatment, the stone-removal effect was significant, and it also indicated once again its advantages of less trauma and rapid postoperative recovery.

To sum up, it is concluded as follows: ESD for the treatment of patients with common bile duct stones is better than EST treatment in reducing surgical stress, optimizing postoperative physical status and other aspects and it's worth popularization and application in clinical practice in the future.

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