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To evaluate the correlation between the change of immune system function before and after the treatment of malignant obstructive type jaundice treated with biliary stent

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Abstract. – OBJECTIVE: To evaluate the correlation between the change of immune system function before and after the treatment of malignant obstructive type jaundice (MOJ) treated with a biliary stent.

PATIENTS AND METHODS: 148 patients who were admitted to the Department of Digestive System for malignant obstructive jaundice were selected according to the standardized criterion. Amongst the total sample size, 78 were male patients and 70 were female patients, with an average age of (43.6 ± 5.5) years. After admission, the patients completed the blood routine examination and received biliary stent treatment to relieve the sign and symptoms of jaundice. Follow-up observation included total white blood cells, CD4+T cell count, CD8+T cell count, the ratio of CD4+/CD8, neutrophil counts neutrophils percentage, total bilirubin, free bilirubin, alanine aminotransferase (ALT), and inflammatory factors.

RESULTS: After three weeks of follow-up visit, CD4+T lymphocyte absolute value of patients markedly increased compared with that of pre-operation, and the difference had statistical significance ($p < 0.05$). The total bilirubin, free bilirubin, ALT, and inflammatory factors, such as hs-CRP, TNF-α in plasma of patients was significantly lower than that before the operation and the difference was statistically significant ($p < 0.05$). After six weeks of follow-up visit, the ratio of CD4+/CD8+ increased and the difference had statistical significance ($p < 0.05$) compared with that before biliary stent implantation. However, the white blood cell and neutrophil granulocyte did not improve significantly. It was found that CD4+/CD8+T lymphocyte had relation with the level of hs-CRP.

CONCLUSIONS: The patients with the (MOJ) treated with implanted biliary stent revealed relive in the obstruction of biliary the tract, which will further significantly improve the cholestasis. The ratio of CD4+/CD8+T lymphocyte increased, which will improve the immune system function of the patients, decreases the possibility of infection, and improves the overall survival quality.

Key Words:

Malignant obstructive jaundice, Biliary stent, Immune function, Cholestasis, CD4+/CD8+T lymphocytes.

Introduction

Malignant obstructive jaundice (MOJ) comprises the group of diseases that can be caused by primary biliary and extra-biliary carcinomas. Generally, surgical resection is the primary treatment for malignant obstructive jaundice. However, for the patients that are unable to undergo surgery, urgent treatment is required to improve the hepatic function. Nowadays, the main therapeutic method is to treat the malignant obstructive jaundice by the biliary stent implantation[1-3]. Because of the serious infective complications in perioperative stage after the biliary stent implantation, the patients often died from the adverse factors which include low immunity, intestinal mucosal barrier damage, intestinal juice reflux etc[4,5]. In recent years, the incidence rate of MOJ is increasing gradually. Once infection occurs, it is very convenient to cause the multiple organ dysfunction syndrome (MODS)[6]. Most of the patients with MOJ who were treated with biliary stent implantation were in the older age group and among those having extremely low immunity. Further, the jaundice can induce the damage of intestinal mucosal barrier and alteration of intestinal flora. So, the effect of anti-infection treatment in MOJ with biliary stent implantation is considered to

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be poor most of times. There are many of the patients with end-stage MOJ diagnosed in China, so a large number of medical resources were consumed because of infection after biliary stent implantation every year[7-9].

MOJ is a series of clinical symptoms[3,4] caused by the obstruction of internal and external bile duct due to the growth and infiltration of hepatobiliary and pancreatic malignant tumor. At present, percutaneous transhepatic cholangial drainage (PTCD) and biliary stent implantation have become the main palliative treatment method for the end-stage malignant obstructive jaundice[10-12]. The percutaneous trans-hepatic cholangial drainage along with biliary stent implantation has the advantages of small damage, high success rate and positive effect of relieving jaundice[13]. However, literature suggests many postoperative complications of this method such as postoperative infection, hemorrhage, bile leakage, pancreatitis and so on. The occurrence rate of the post-operative complication can reach up to 30-50%[14] and the endotoxemia can reach up to 50-80%[14,15]. Low immunity and damage of intestinal mucosal barrier caused by MOJ can lead to intestinal bacteria translocation and retrograde infection after the biliary stent implantation, which will further result in release of intestinal endotoxin into blood and postoperative serious sepsis which finally leads to MODS. So, because of MODS, the several patients die in perioperative period[16-18].

How to effectively reduce the occurrence of postoperative complications of MOJ infection is the key to improve the efficiency of surgical treatment[7]. So, the objective of the study was to evaluate the correlation between the change of immune system function before and after the treatment of malignant obstructive type jaundice (MOT) treated with biliary stent.

Patients and Methods

Patients

The total sample size was comprised of 148 patients who were admitted to the Department of Digestive System of our hospital for MOJ. Out of which 78 were male patients and 70 were females patients, with the average age of (43.6 ± 5.5) years old. The course of disease lasting for 3-5 years, with average course of disease for (2.7 ± 1.3) years. The general data of patients when they were admitted to hospital have been shown in Table I. This study was approved by the Institutional Ethics Committee of our hospital. The informed consent signed by patients and/or their families was obtained.

Diagnostic, Inclusion, and Exclusion Criteria

Diagnostic criteria: Biochemical index – Total bilirubin exceeded the upper limit of normal value, with direct bilirubin/total bilirubin > 50%; iconography index: with or without extrahepatic bile duct expansion in hepatic space with extrahepatic bile duct invaded or oppressed manifestation; other index: positive urine bilirubin, kaolin stool.

Inclusion criteria: Patients of MOJ diagnosed by clinical or pathological examination, patients that need treatment without excision, patients willing to conduct percutaneous transhepatic stent implantation. The informed consent signed by patients were included in the study group.

Exclusion criteria: Patients that had duodenal obstruction and could not take orally before operation, patients having past history of failed biliary stent placement, patients whose state of illness was aggravated due to hemobilia or other non-infection causes, patients with hypohepatia caused by biliary obstruction combined with primary hepatic disease including virus hepatitis. Patients with severe heart, lung, kidney diseases. Patients who discharged in advance and refused to continue different examination and treatment were excluded from the study group.

Table I. Clinical basic features comparison of 148 patients with malignant obstructive jaundice.

Gender		Age	Time of operation (t/min)	Amount of bleeding during operation (V/ml)	Hospital stay (t/d)	Interval between admission to opera-tion (t/min)
Male	Female					
78	70	61.8 ± 4.6	45.2 ± 12.6	56.4 ± 4.7	6.8 ± 1.3	70.5 ± 23.6

Routine Blood Detection Method

4-6 ml of sterile whole blood were taken from a vein, with routine detection of peripheral white blood cell and neutrophil granulocyte. The quantitative detection and analysis of T lymphocyte subsets was tested by monoclonal antibody mensuration.

HbA1c Detection

4-6 ml of peripheral venous blood was taken from the patients, with the detection by Variant II hemoglobinometer (Bio-Rad, Hercules, CA, USA).

With the help of a portable glucometer (Medtronic, Minneapolis, MN, USA), the fasting blood-glucose (FBG) was detected.

Other Biochemical Criterion Detection

4-6 ml of sterile whole blood was taken, and other biochemical criterion detections such as blood fat and aminotransferase (ALT) were measured by Roche modular fully automatic biochemical analyzer (Indianapolis, IN, USA). CRP detection was done by immuno-turbidimetery (Zhongshan Jinqiao Company, Shanghai, China), and enzyme-linked immunosorbent assay (kit bought from Genzyme Company (Cambridge, MA, USA) was applied for the detection of TNF-α, IL-1β, IL-6, IL-8.

Biliary Stent Implantation

(1) Detection of stomach or duodenum puncture point was located with the application of Doppler ultrasonography. (2) Endoscopic Ultrasound (EUS)/Fine Needle Aspiration (FNA) technology was applied after stylet removal to puncture the biliary tract and further, guide wire was placed through puncture needle at the proper location. (3) Choice of puncture needle: 19 G or 22 G puncture needle. 19 G can pass through the guide wire of 0.035 inches, while 22 G version can pass through the guide wire of 0.018 inches. (4) Guide wire was entered into the duodenal papilla through stenosis; then, the needle shell and ultrasonic endoscopic procedures were carried out. (5) Duodenoscope reached up to the duodenal papilla along with the guide wire. When the intubation tube succeeded, guide wire was pulled out by biopsy forceps or endloop through endoscope working channel. (6) The guide wire after puncture was dragged out from the mouth and passed through the working channel of duodenoscope. (7) At last, biliary stent was implanted to proceed with the drainage.

Statistical Analysis

SPSS 19.0 (SPSS Inc., Chicago, IL, USA) was applied to statistical treatment and analysis in this study. ANOVA was used for the correlation analysis of quantitative data. The χ^2-test was applied to test the qualitative data. Fisher method was used to calculate the accurate probability. Logistic Regression Analysis was adopted to correlate the relevance between postoperative immune function change and infection of biliary tract. p-value of less than 0.05 was considered as statistically significant.

Results

Statistical analysis of T-lymphocyte subset of patients ($\bar{x} \pm s$): total white blood cells, total neutrophil granulocyte, total lymphocyte count, CD4+ cell count, CD8+T cell count, and CD8+T cell percentage of postoperative patients from each follow-up visit were conducted with statistical analysis. It was found that the change of CD4+T lymphocyte count and its percentage, as well as the ratio of CD4+/CD8+, was proved to be statistically significant ($p = 0.02$) after 6 weeks (Table II).

Table II. Statistical analysis of T-lymphocyte subset of patients ($\bar{x} \pm s$).

Items	Numbers of cases (no.)	On admission	3 weeks after operation	6 weeks after operation	F-value	*p*-value
CD4+T Lymphocyte Counts (/μL)	148	421.7 ± 102.5	412.6 ± 79.3	669.4 ± 102.4	10.23	0.02
CD4+T Lymphocyte Counts (%)	148	37.4 ± 14.3	55.6 ± 14.7	58.9 ± 12.6	2.24	0.02
CD8+T Lymphocyte Counts (/μL)	148	337.3 ± 64.5	435.7 ± 35.8	473.2 ± 56.4	0.87	0.39
CD8+T Lymphocyte Percentage (%)	148	430.4 ± 102.4	521.7 ± 111.2	1489.4 ± 148.4	0.97	0.33
CD4+/CD8+	148	0.71 ± 0.21	0.89 ± 0.24	2.37 ± 1.09	21.74	0.01

Table III. Statistical analysis of results of white blood cell count, neutrophil count and neutrophilic granulocyte percentage from each postoperative. Follow-up visit ($\bar{x} \pm s$).

Items	Numbers of cases (no.)	3 weeks after operation	6 weeks after operation	F-value	*p*-value
White blood cell count ($\times 10^9$/L)	148	9.87 ± 2.32	7.85 ± 1.13	0.36	0.77
Neutrophil count ($\times 10^9$/L)	148	6.87 ± 0.86	7.42 ± 0.21	0.76	0.82
Neutrophilic granulocyte percentage (%)	148	72.4 ± 8.64	73.2 ± 6.32	0.74	0.57

Results of white blood cell count, neutrophil count and neutrophilic granulocyte percentage from postoperative follow-up visits ($\bar{x} \pm s$): after the procedure of biliary stent implantation, the results of white blood cell count, neutrophil count, and neutrophilic granulocyte percentage were analyzed statistically, and the difference had no statistical significance with *p*-value of more than 0.05 (Table III).

Inflammatory factors and biochemical criterion of postoperative follow-up visits: the inflammatory factors and biochemical criterion of postoperative patients were recorded and analyzed statistically. It was found that the indexes level including hs-CRP, TNF-α, Il-1β, Il-6, Il-8 of patients after 6 weeks of operation were drastically decreased compared to the previous treatment. The difference was of statistical significance ($p < 0.05$). The serum creatinine, serum total bilirubin, ALT, blood amylase of the patients reduced significantly compared with those before treatment with signficant *p*-value of less than 0.05 (Tables IV, V).

Correlation analysis of infection risk factors after biliary stent implantation: Logistic Regression Analysis was applied to the multiple risk factors after biliary stent implantation. The risk factors included gender, age, SBP (mmHg), DBP (mmHg), AST (U/L), ALT (U/L), logGGT (U/L), FPG (mmol/L), BMI (kg/m^2), WBC ($\times 10^9$/L), Scr (μmol/L), BUN (mmol/L), TBIL (μmol/L), AMS (U/L), Hs-CRP (mg/L), TNF-α (pg/mL), IL-1β (pg/mL), IL-8 (pg/mL), IL-6 (pg/mL), neutrophil count ($\times 10^9$/L), neutrophilic granulocyte percentage (%), CD4+T lymphocyte count (/μL), CD4+T lymphocyte percentage (%), CD8+T lymphocyte count (/μL), and CD8+T lymphocyte percentage (%). The results indicated that Hs-CRP level had a negative correlation with CD4+/CD8+ level, with correlation coefficient r = -1.027, $p < 0.05$ (Tables VI, VII, VIII, IX).

Table IV. Inflammatory factors and biochemical criterion of postoperative follow-up visits.

Items	Numbers of cases (no.)	Before treatment	3 weeks after operation	6 weeks after operation	F-value	*p*-value
Hs-CRP (mg/L)	148	217.6 ± 23.4	168.7 ± 10.8	91.2 ± 3.1	12.83	0.03
TNF-α (pg/mL)	148	647.9 ± 201.3	1004.5 ± 121.7	921.7 ± 22.8	18.45	0.01
IL-1β (pg/mL)	148	728.4 ± 21.8	403.4 ± 22.8	271.6 ± 12.7	29.4	0.01
IL-6 (pg/mL)	148	602.4 ± 31.7	315.4 ± 12.9	104.7 ± 21.7	12.8	0.02
IL-8 (pg/mL)	148	602.3 ± 22.3	366.4 ± 12.7	217.3 ± 8.2	10.6	0.02

Table V. Change of biochemical criterion before and after treatment.

Items	Numbers of cases (no.)	Before treatment	3 weeks after operation	6 weeks after operation	F-value	*p*-value
Scr μmol/L	32	439.4 ± 38.6	377.3 ± 32.4	236.5 ± 50.7	3.89	0.02
BUN mmol/L	32	27.4 ± 13.4	18.3 ± 3.4	14.4 ± 23.5	17.65	0.01
TBIL μmol/L	32	56.4 ± 21.8	77.8 ± 23.5	78.4 ± 12.7	12.48	0.01
ALT U/L	32	91.4 ± 21.5	69.4 ± 13.3	47.3 ± 12.8	10.08	0.01
AMS U/L	32	817.8 ± 212.5	611.3 ± 1.4	510.3 ± 1.3	10.87	0.02

Table VI. Correlation analysis between CD4+/CD8+ and clinical detection index.

Index	Gender	Age	SBP mmHg	DBP mmHg	AST U/L	ALT U/L	logGGT U/L	FPG mmol/L	BMI kg/m²
CD4+/CD8+									
r	0.022	0.351	0.116	0.328	0.124	0.415	0.106	0.238	0.114
p	> 0.05	> 0.05	> 0.05	> 0.05	> 0.05	> 0.05	> 0.05	> 0.05	> 0.05

Table VII. Correlation analysis between CD4+/CD8+ and clinical detection index.

Index	WBC × 10^9/L	Scr μmol/L	BUN mmol/L	TBI-L μmol/L	AMSU/L	Hs-CRP mg/L	TNF-α/ pg/mL	IL-1β pg/mL	IL-8 pg/mL	IL-6 pg/mL
CD4+/CD8+										
r	-0.021	-0.351	-0.161	-0.482	-0.283	-1.027	1.063	-0.381	-0.191	-0.141
p	> 0.05	> 0.05	> 0.05	> 0.05	> 0.05	< 0.05	< 0.05	> 0.05	> 0.05	> 0.05

Table VIII. Correlation analysis between CD4+/CD8+ and clinical detection index.

Index	Neutrophil count (×10^9/L)	Neutrophilic granulocyte percentage (%)	CD4+T lymphocyte count (/μL)	CD4+T lymphocyte count (%)	CD8+T lymphocyte count (/μL)	CD8+T lymphocyte count (%)
CD4+/CD8+						
r	0.02	0.35	0.16	0.28	0.24	0.15
p	> 0.05	> 0.05	> 0.05	> 0.05	> 0.05	> 0.05

Table IX. Multiple linear regression analysis.

Variable quantity	β	SE	β′	*t*	*p*	(95% CI) Upper limit	(95% CI) Lower limit
TNF-α (pg/mL)	0.521	0.08	0.632	0.652	> 0.05	0.49	0.88
Hs-CRP (mg/L)	0.798	0.04	0.851	0.981	< 0.05	0.51	0.82

Discussion

Studies reveal that the biliary stent implantation for MOJ might increase the prevalence rate of infection due to various reasons such as biliary retrograde infection, low immunity of organism, damage of intestinal mucosal barrier, and so on. In this study, it was found that three weeks after the implantation, CD4+T lymphocyte count of the patients markedly increased compared with that of pre-operation, and the difference had statistical significance value ($p < 0.05$). After the six weeks of follow-up visit, the ratio of CD4+/CD8+ increased and the difference had statistical significance ($p < 0.05$) compared with that before the biliary stent implantation. However, the white blood cell and the neutrophil granulocyte count did not improve significantly through the detection of various infection index after the biliary stent implantation. We hold that the drainage tube and stent will connect with the outside with the intestinal tract, with regurgitation of intestinal juice after percutaneous trans-hepatic biliary drainage and biliary stent implantation, which further cause retrograde infection of biliary tract easily and the bile will become a favorable culture medium. The immune function of these patients who has suffered from some strikes such as chemoradiotherapy besides tumor impact, malnutrition, hyperbilirubinemia, and endotoxemia is inhibited. We speculated that, when the biliary tract was obstructed and bile was insufficient

within biliary tract, the lymphocyte of intestinal mucosa lamina propria including IgA, CD4 and CD8 reduced[6-8]. This leads to the reduction of intestinal juice secreting type IgA concentration, which further decline the immune function of biliary tract resulting in the bacterial translocation easily[7,8]. Some reports also revealed that cell factors also play an important role in this process, and endotoxin can stimulate macrophage to generate tumor necrosis factor (TNF), inhibiting the immune function of host cells through TNF[7].

Also, it was found that, after the three weeks of biliary stent implantation, total bilirubin, free bilirubin, ALT, and inflammatory factors, such as hs-CRP, TNF-α and Il-6 in plasma of patients was significantly lower than that before the operation, and the difference was statistically significant ($p < 0.05$). Research studies have concluded that inflammatory mediator plays a critical function in MOJ. Prostaglandin E (PGE) in inflammatory mediator can restrain T lymphocyte from generating interferon (INF) and interleukin 2 (IL-2), inhibit T lymphocyte proliferation and the activation of T lymphocyte subsets which further leads to decline the activity of NK cells[16]. Moreover, the endotoxins can damage the systemic function of mononuclear phagocyte and the activity of intrahepatic Kupfer cells became limited, with the decline of phagocytic ability, killing activity, and immune function[17]. Some researches in recent years pointed that both of inflammatory reaction and immune dysfunction are the central parts of traumatic (including surgical strikes) sepsis and the incidence and development of MODS.

We also found that the high risk factors of immunity dysfunction caused by malignant biliary obstruction are blood glucose levels, glycosylated hemoglobin, ALT, AST, LDL-C, HDL-C, triglyceride, hs-CRP, neutrophil count, neutrophilic granulocyte percentage, T lymphocyte count and level, tumor size of biliary tract[1-4,6,8,12-14]. Logistic Regression Analysis have revealed that the ration of CD4+/CD8+T lymphocyte had a relation with the level of serum hs-CRP, with the correlation coefficient r = -1.027 with significant $p < 0.05$. The study suggested that the level of hs-CRP has a positive correlation with the ratio of peripheral blood CD3+ and CD4+ T lymphocyte. Therefore, with the combination of results in this study, we concluded that it is necessary to regulate the levels of hs-CRP, inflammatory cell infiltration and the inflammatory factors, so as to improve the postoperative infection by medicine after malignant obstructive jaundice[16-18]. When malignant obstructive jaundice occurs, intestinal mucosa chemical barrier will be damaged due to insufficient bile. If there are insufficient bile salts, the patients cannot absorb nutrition substance in accurate amount which will lead to the atrophy of intestinal mucosa. This will also affect the intestinal mucosa morphology and reduce the muscle transmural electricity[19]. The literature suggests that, in malignant obstructive jaundice, there will be thinning of ileum mucosa with blunter villus, less density of epithelium, subepithelial edema, and epithelial layer will be separated from the lamina propria. Under the electric microscope, it can be seen that partial epithelial detach with endochylema vacuolation, phagolysis formation, breakage of intercellular tight junction, swollen granules and loss of cristae, which will lead to the damage of mechanical barrier[20,21].

Conclusions

Patients with the MOJ treated with implanted biliary stent revealed relive in the obstruction of biliary tract, which will further significantly improve the cholestasis. The ratio of CD4+/CD8+T lymphocyte increased, which will improve the immune system function of the patients, decrease the possibility of infection, and improve the overall survival quality of patients.

Conflict of Interest

The Authors declare that they have no conflict of interests.

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