

Effects of different drainage procedures on levels of serum endotoxin and tumor necrosis factor in patients with malignant obstructive jaundice

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OBJECTIVE: To assess the influence of different drainage procedures on the levels of serum endotoxin and tumor necrosis factor (TNF) in patients with malignant obstructive jaundice (MOJ).

METHODS: The levels of endotoxin and TNF in 46 patients with MOJ were measured before and after cholangiojejunostomy (CJ) or external bile drainage (EBD).

RESULTS: In the CJ group, the levels of postoperative serum endotoxin and TNF 10 days after operation were significantly lower than those before operation ($P < 0.01$). In the EBD group, no significant changes were observed in endotoxin and TNF levels before and after operation ($P > 0.05$). No significant differences were seen between the two groups before operation ($P > 0.05$), but the levels of endotoxin and TNF in the CJ group were significantly lower than those in the EBD group after operation ($P < 0.01$).

CONCLUSIONS: Cholangiojejunostomy other than external bile drainage can decrease the levels of serum endotoxin and TNF effectively, although both of them are able to release jaundice.

Cholangiojejunostomy should be performed as soon as possible for patients with unresectable malignant tumor.

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Key words: cholestasis; endotoxin; tumor necrosis factor; bile duct neoplasm

Introduction

It is the conventional concept that the high level of serum bilirubin may cause multisystemic damage to the body of the patients with obstructive jaundice. If malignant neoplasm is found unresectable at the time of operation, jaundice release should be the prime purpose. Current pathophysiological studies on obstructive jaundice have shown

that the damage to the liver, kidney, and immune system of the patients are closely related to endotoxaemia. In this process, serum endotoxin plays an important role, but endotoxin influence is dependent on the increase of endotoxin-induced tumor necrosis factor (TNF). The aim of this study was to assess the influence of different drainage procedures on the recovery of physical conditions of patients with malignant obstructive jaundice (MOJ). We compared the levels of serum endotoxin and TNF in 46 patients with MOJ before and after operation.

Methods

Patients

From January 1997 to December 2000, 46 patients

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with MOJ were treated at our hospital. Bile duct carcinoma was found in 12 patients, Vater ampullar carcinoma in 3, and pancreatic head carcinoma in 31. The tumors were unresectable, and were confirmed pathologically by operative biopsy. In these patients, 30 were male and 16 female, aged on average of 50 years (range 22–76). Their jaundice duration ranged from 12 to 80 days. Eighteen patients underwent external bile drainage (EBD), and the other 28, cholangiojejunostomy (CJ).

Methods

3–5 ml of venous blood after fasting was taken on the day before operation and the 3rd, 10th, and 30th day after surgery, respectively. The specimens were kept at -20 °C in a refrigerator, and assayed later. Endotoxin was tested using Limulus reagents and tripeptide azo color-developing process (reagents from Shanghai Medical Assay Institute, Shanghai, and 721-type spectrophotometer). TNF was examined by radioimmunoassay (RIA), with reagent kits purchased from the Chinese Atomic-energy Research Institute, Shanghai, China. Double-blinding was adopted in this study.

Statistical analysis

Student's *t* test was used.

Results

Equilibrium between CJ and EBD groups

No significant differences were seen in age, jaun-

Table 1. Test for equilibrium between CJ and EBD groups

Group	<i>n</i>	Mean age (y)	Mean jaundice duration (d)	Bilirubin level before operation (μmol/L)	30th day bilirubin level after operation (μmol/L)
CJ	28	50.1 ± 6.5	25.0 ± 7.5	272.5 ± 88.0	45.8 ± 11.6
EBD	18	49.2 ± 7.9	24.0 ± 9.0	269.8 ± 71.5	40.1 ± 12.0
<i>P</i> >		0.50	0.50	0.40	0.40

dice duration, and serum bilirubin (BIL) level on average the day before operation and 30th day post-operation between the two groups (*P* > 0.05, Table 1).

Levels of endotoxin

In the CJ group, the mean level of serum endotoxin on the day before operation was not significantly different from that on the 3rd day postoperation (*P* > 0.05), but that on the 10th or 30th day postoperation (*P* < 0.01 or *P* < 0.001). On the day before operation and the 3rd day postoperation, the mean levels of serum endotoxin were not markedly different between the EBD and CJ group (*P* > 0.05). On the 10th and 30th day postoperation, however, the level of endotoxin of the CJ group was markedly lower than that of the EBD group (*P* < 0.05, *P* < 0.001). In the EBD group, the level of endotoxin before surgery was not significantly different from that on the 3rd, 10th, or 30th day postoperation (*P* > 0.05, Table 2).

Table 2. Levels of endotoxin in CJ and EBD groups pre- and postoperation (Eu/ml)

Group	<i>n</i>	First day preoperation	3rd day postoperation	10th day postoperation	30th day postoperation
CJ	28	0.75 ± 0.22	0.59 ± 0.18 ^Δ	0.45 ± 0.18 [#]	0.30 ± 0.08 [#]
EBD	18	0.70 ± 0.25 [*]	0.58 ± 0.24 ^{*Δ}	0.61 ± 0.12 ^{Δ**}	0.69 ± 0.09 ^{Δ**}

* *P* > 0.05 compared with CJ; ^Δ *P* > 0.05 compared with preoperation; ** *P* < 0.05 compared with CJ; [#] *P* < 0.05 compared with preoperation.

Table 3. Mean TNF levels in CJ and EBD groups pre- and postoperation (μmol/L)

Group	<i>n</i>	First day preoperation	3rd day postoperation	10th day postoperation	30th day postoperation
CJ	28	2.25 ± 0.50	2.25 ± 0.68 ^Δ	1.25 ± 0.33 [#]	0.94 ± 0.19 [#]
EBD	18	2.43 ± 0.57 [*]	2.44 ± 0.69 ^{*Δ}	2.34 ± 0.61 ^{Δ**}	2.21 ± 0.58 ^{Δ**}

* *P* > 0.05 compared with CJ; ^Δ *P* > 0.05 compared with preoperation; ** *P* < 0.05 compared with CJ; [#] *P* < 0.05 compared with preoperation.

Levels of TNF

In the CJ group, the mean level of serum TNF on the day before operation was not significantly different from that on the 3rd day postoperation ($P > 0.05$), but the level on 10th and 30th day postoperation were notably lower than those before operation ($P < 0.01$ or $P < 0.001$). On the day before operation and the 3rd day postoperation, the mean levels of serum TNF were not significantly different between the EBD and CJ group ($P > 0.05$). On the 10th and 30th day postoperation, however, the TNF levels of the CJ group were markedly lower than those of the EBD group ($P < 0.05$, $P < 0.001$). In the EBD group, the preoperative TNF levels were not significantly different from those on the 3rd, 10th, or 30th day ($P > 0.05$, Table 3).

Discussion

Lots of endotoxin exist in the gastrointestinal tract in which there are abundant gram-negative bacteria. Endotoxin in the intestine is least absorbed to the blood circulation normally. Studies have demonstrated that the higher incidence of endotoxaemia in patients with obstructive jaundice is related to many risk factors. Biliary tract obstruction results in less bile in the intestine, thereby the absence of bile salt promotes the overgrowth and translocation of bacteria, and failure to neutralize or degrade endotoxin by bile salt.^[1] Intestinal permeability is significantly increased in patients with jaundice compared with normal persons. Obstructive jaundice is related to impaired gut barrier function and activation of host immune function that is exacerbated by intervention.^[2] The bile is thought to protect intestinal mucosal barrier function. Hence the integrity of the intestinal mucosal barrier is of paramount importance in preventing bacterial translocation, and the measures taken to protect the mucosal integrity for lowering bacterial translocation are more important than those for decreasing the number of bacteria in the gut. Significant bacterial translocation has been identified after choledochal obstruction and that in jaundiced animals the total

mucosal thickness is significantly reduced. In enterocytes, moreover, vacuolation of their cytoplasm and mitochondrial swelling occur with increased numbers of bacteria attached to the mucosa.^[1,3] Biliary tract obstruction can cause damage to liver cells and thus alter their function, and further Kupffer cell function, which may be independent on the effects of bacterial translocation.^[4] The inhibition of Kupffer cells may improve the survival of patients and suppress TNF activity. In patients with obstructive jaundice, hypersecretion of TNF by Kupffer cells may support the production of systemic cytokine and be responsible for significant complications.^[5] Our data have shown that the level of serum endotoxin is markedly higher in patients with malignant obstructive jaundice, and different drainage procedures can produce some improvement of endotoxaemia. In the CJ group of our study, the level of serum endotoxin after operation decreased significantly compared with that before operation; in the EBD group, however, no significant difference was observed before and after operation. Endotoxaemia in the CJ group was not different from that of the EBD group before operation. Ten days after surgery, the remission rate of endotoxaemia in the CJ group was better than in the EBD group. Another study found that EBD could not relieve endotoxaemia, and after EBD the risk for infective complications increased.^[6] In a word, bile in the gut is essential to elimination of endotoxin.

TNF, a kind of cytotoxic protein, is produced by monocytes and macrophagocytes because of the activation of bacterial endotoxin, tissue injury, or tumor cells. Endotoxin is a strong substance to stimulate the production of TNF. As a medium, TNF takes part in sepsis and host immunoreaction. The mechanism of immunologic inadequacy in patients with obstructive jaundice has not yet been clarified. But previous studies demonstrated its existence by the test of humoral and cytoimmunologic index.^[2] Obstructive jaundice sensitizes macrophage-rich organs to produce larger amounts of TNF-alpha in response to endotoxin. This sensitization is not solely due to decreased intraluminal gut bile.^[7] Excessive production of hydroxyl and superoxide radicals in

blood and the liver has been detected in rats with obstructive jaundice induced by the ligation of the common bile duct (CBDL). To pinpoint the molecular agents that mediate these processes, Liu et al^[8] measured circulating proinflammatory cytokines, such as TNF-alpha in controls and CBDL rats. TNF-alpha concentrations in blood of the CBDL rats were markedly elevated when compared to the controls. They found the overproduction of free radicals triggered by elevated cytokines was correlated with the activation of NF-kappaB in the hepatic tissue. They noted that sections of the hepatic tissue from the CBDL rats showed an increase in the apoptotic index. The severe hepatic injury in the CBDL rats was mediated by a cycle that involves the activation of NF-kappaB by combined action of proinflammatory cytokines and reactive oxygen species.^[9] We found that the preoperative levels of serum TNF were increased in the CJ and EBD patients with malignant obstructive jaundice. From the 10th day after surgery, the level of serum TNF decreased significantly in the CJ group, but not in the EBD group. This is possibly due to the reduction of endotoxin, not due to bilirubin release. Because 30 days after drainage, the levels of serum bilirubin were no significantly different between the two groups, but the levels of serum TNF in the CJ group were markedly decreased compared to the EBD group. Dawiskiba et al^[9] reported the same result.

In conclusion, endotoxaemia may increase the level of serum TNF. TNF overproduction can cause injury to the tissue and increase the risk of infective complications. It is closely related to the impairment of immunologic function. Hence, the treatment of endotoxaemia is more important than jaundice release in patients with malignant obstructive jaundice. If the tumor is unresectable and palliative surgery is advisable intraoperatively, cholangiojejunostomy should be adopted as soon as possible. High level of serum TNF may not only cause injury to immunologic function but also prevent wound healing in patients with obstructive jaundice.^[10] Researchers^[11] reported that obstructive jaundice leads to increased production of endotoxin-induced TNF-alpha which can be inhibited

by the replacement of intestinal bile acid. Another finding is that the intravenous administration of ursodeoxycholic acid can prevent endotoxaemia.^[12] We suggest that patients with carcinoma of the bile duct who are intolerable to cholangiojejunostomy, oral or intravenous bile salt should be prescribed after operation.

Competing interest

No benefits in any form have been received or will be received from a commercial party related directly or indirectly to the subject of this article.

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