Endotoxemia after Abdominal Surgery

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NAKAGAWA, K., MATSUBARA, S., OUCHI, K., OWADA, Y. and YAJIMA, Y.
Endotoxemia after Abdominal Surgery. Tohoku J. exp. Med., 1986, **150** (3), 273-
280 — The blood level of endotoxin after operations in patients with digestive
diseases, mainly liver cirrhosis and obstructive jaundice, and the complications
most likely related to the presence of endotoxemia were investigated. Twenty-
seven patients without either liver cirrhosis or obstructive jaundice showed a
minimal elevation of the endotoxin level in blood, as shown by 6.1 ± 3.9 (mean $\pm$
s.e.) pg/ml at the first postoperative day and there was only one anastomotic
leakage. On the other hand, 18 patients with liver cirrhosis showed a notable and
persistent endotoxemia after surgery. The cirrhotic patients who especially
underwent splenectomy and hepatectomy showed marked elevations of endotoxin
level at the first postoperative day, with values of 151.0 ± 46.1 pg/ml and $101.3 \pm$
 36.2 pg/ml, respectively, and one of these patients died of hepatic failure.
Thirteen patients with obstructive jaundice developed endotoxemia evidenced by
the value of 21.6 ± 4.8 pg/ml at the first day after surgery. Among these patients,
two had gastrointestinal bleeding and one developed disseminated intravascular
coagulation (DIC). The markedly high and persistent levels of endotoxin in
patients with liver cirrhosis or obstructive jaundice may be possibly related with
the development of multiple organ failure (MOF). ————— endotoxemia; surgical
complications; liver cirrhosis; obstructive jaundice; reticuloendothelial system

The postoperative course in patients with liver cirrhosis or obstructive jaun-
dice is frequently eventful because the incidence of major complications such as
hyperpyrexia, respiratory failure, gastrointestinal bleeding, DIC, renal failure,
and liver failure is not so uncommon (Lindenmuth and Eisenberg 1963). Recent-
ly, in relation to the explanation of such an eventful postoperative course,
increasing attention has been paid to the presence of endogenous endotoxemia
(Wilkinson et al. 1976; Tarao et al. 1977). Because in the past the detection of
endotoxin in blood has been largely based on qualitative assay with the Limulus
gelation test, it was highly difficult to follow the changes of postoperative endotox-

Received July 8, 1986; accepted for publication September 29, 1986.

Abbreviations: DIC, disseminated intravascular coagulation; MOF, multiple organ
failure; PTBD, percutaneous transhepatic biliary drainage.

emia precisely. The recent development of a new technique to detect endotoxin using chromogenic substrates has made it possible to elucidate the quantitative changes of small amounts of endotoxin in blood. The present study was undertaken to investigate the changes of blood endotoxin levels after abdominal surgery, mainly in patients with liver cirrhosis or obstructive jaundice, and to discuss the relation of the occurrence of postoperative complications.

PATIENTS and METHODS

As shown in Table 1, 58 patients were subjected to this study. The level of blood endotoxin was assayed in three groups of patients, control (27 cases), liver cirrhosis (18 cases), and obstructive jaundice (13 cases). The control group was the patients underwent gastrectomy (9 cases), cholecystectomy (4 cases), colectomy (5 cases), and hepatectomy (9 cases). The liver cirrhosis group consisted of patients who underwent upper abdominal surgery without splenectomy (4 cases), upper abdominal surgery with splenectomy (5 cases), and hepatectomy (9 cases). The operations in the obstructive jaundice group included pancreaticoduodenectomy (3 cases), choledochojejunostomy (9 cases), and choledocholithotomy (1 case).

The blood samples for the measurement of endotoxin were aseptically taken with heparinized syringes prior to surgery, or in the group of obstructive jaundice, just before the biliary drainage, and subsequently at the 1st, 3rd, 7th, 14th, and 21st postoperative day. The samples were centrifuged at $150 \times g$ for 10 min, and the supernatants (the platelet rich plasma) were stored at -80°C . Endotoxin was assayed using the Limulus Colorimetric Test (Toxicolor Test, Seikagaku-kogyo, Tokyo) with the perchloric acid pretreatment.

All data were expressed as mean $\pm$ s.e. and the statistic significance of difference was evaluated according to Student's *t*-test. Differences were judged to be significant when *P* values were less than 0.05.

TABLE 1. *Classification of the subjects*

	Operation method	Number	Complication
Control (<i>n</i> = 27)	Gastrectomy	9	Anastomotic leakage 1
	Cholecystectomy	4	
	Colectomy	5	
	Hepatectomy	9	
Liver cirrhosis (<i>n</i> = 18)	Upper abdominal surgery without splenectomy	4	Anastomotic leakage 1 Hepatic failure 1
	Upper abdominal surgery with splenectomy	5	
	Hepatectomy	9	
Obstructive jaundice (<i>n</i> = 13)	Pancreaticoduodenectomy	3	Gastrointestinal bleeding 2 DIC 1
	Choledochojejunostomy	9	
	Choledochostomy	1	

RESULTS

Control group

The average value of endotoxin prior to operation was 4.2 ± 1.0 pg/ml. No significant difference was seen in between each type of diseases (Fig. 1). The cases of gastrectomy, cholecystectomy, and colectomy showed minimal increases of endotoxin levels at the first day after surgery, which returned to the preoperative values at the third day. On the other hand, the case of hepatectomy showed the elevation of endotoxin level of 18.3 ± 8.8 pg/ml at the first day, which was still higher than the preoperative value even at the 14th day. As a complication of surgery, one case showed an anastomotic leakage with a concomitant re-elevation of the level of endotoxin, 23 pg/ml at the 7th day, and it reduced in accordance with the improvement of clinical symptoms.

Liver cirrhosis group

The preoperative value of endotoxin in the liver cirrhosis group was 4.5 ± 1.1 pg/ml, being slightly higher than that of the non-cirrhotic group (Fig. 2). However, the value of endotoxin increased significantly after operation compared to the control group and the increased level was sustained for a certain period.

Fig. 1. Changes of endotoxin levels after operation in patients without either liver cirrhosis or obstructive jaundice. Data points are means $\pm$ s.e. ●—●, hepatectomy (9 cases); △—△, colectomy (5 cases); ×—×, gastrectomy (9 cases); ○—○, cholecystectomy (4 cases).

Fig. 2. Changes of endotoxin levels after operation in patients with liver cirrhosis. Data points are means $\pm$ s.e. $\blacktriangle$ — $\blacktriangle$, upper abdominal surgery with splenectomy (5 cases); $\circ$ — $\circ$, upper abdominal surgery without splenectomy (4 cases); $\bullet$ — $\bullet$, control (gastrectomy and cholecystectomy in patients without liver cirrhosis, 13 cases). * $p < 0.05$, ** $p < 0.01$ against corresponding values in the control group.

This tendency was more striking in the patients who underwent splenectomy. The endotoxin level was 151.0 ± 46.0 pg/ml at the first day and even at the 14th day it was still 74.5 ± 34.9 pg/ml. There was one case of the incidence of the anastomotic leakage which was coupled with the re-elevation of the endotoxin level, which reached 70 pg/ml and reduced in accordance with the symptomatic improvement.

With respect to the cases of hepatectomy, the elevation of the endotoxin levels was marked and prolonged compared to the control group as evidenced by the values of 101.3 ± 36.2 pg/ml at the first day and 15.3 ± 3.6 pg/ml at the 14th day (Fig. 3). One patient who subsequently died from liver failure on the 27th day showed a prolonged elevation of the endotoxin level. The values of endotoxin showed a tendency to higher levels when the patients received large amounts of blood transfusion because of massive bleeding.

Obstructive jaundice group

The average total bilirubin level was reduced from 15.9 mg/100 ml at hospitalization to 4.3 mg/100 ml by PTBD. The endotoxin level prior to the PTBD was low averaging 3.4 ± 0.4 pg/ml, and it did not significantly change after the relief of jaundice (Fig. 4). However, a marked increase of endotoxin level was

Fig. 3. Changes of endotoxin levels after hepatectomy. Data points are means $\pm$ s.e. $\circ$ — $\circ$, liver cirrhosis (9 cases); $\bullet$ — $\bullet$, control (9 cases).

Fig. 4. Changes of endotoxin levels after operation in patients with obstructive jaundice. Data points are means $\pm$ s.e. $\circ$ — $\circ$, obstructive jaundice (total bilirubin, 5 mg/100 ml or more at operation; 5 cases); $\times$ — $\times$, obstructive jaundice (total bilirubin, smaller than 5 mg/100 ml at operation; 8 cases); $\bullet$ — $\bullet$, control (gastrectomy and cholecystectomy in patients without obstructive jaundice; 13 cases). * $p < 0.05$, ** $p < 0.01$ against corresponding values in the control group.

observed after surgery and this tendency was striking and persistent for a long time when the level of total bilirubin was 5 mg/100 ml or more at operation. Regarding to the postoperative complications there were hemorrhages from gastric ulcer in one case and from stomal ulcer in one case. During these episodes the endotoxin levels showed high values of 19 pg/ml and 91 pg/ml respectively, and they went down according to the clinical improvement. One case complicated with hemobilia after PTBD underwent operative drainage by laparotomy and died of DIC at the 10th postoperative day. At that time the blood endotoxin showed a high level of 27 pg/ml.

DISCUSSION

There have been increasing reports indicating a high incidence of postoperative endotoxemia in cases of liver cirrhosis and obstructive jaundice (Wilkinson et al. 1976; Tarao et al. 1977). In an effort to assay endotoxin in blood, the Limulus Gelation Test has been largely employed in the past (Levin et al. 1970). However, this method somewhat lacks an objectiveness since it is judged qualitatively by the presence of gelation. Furthermore, no consideration has been given to the elimination of either the activator of the gelation, nonspecific amidolytic activity, or the inhibitors of the gel formation. Iwanaga et al. (1978) recently developed the Limulus Colorimetric Test which measures the activity of endotoxin spectrophotometrically and Tamura et al. (1982) devised the pretreatment of the plasma with perchloric acid to eliminate both the amidolytic activities and the inhibitors of the reaction of Limulus lysate. Using these techniques the quantification of endotoxin activity has become possible to the level of some pg/ml (Yajima et al. 1985).

The high incidence of postoperative endotoxemia in the cases of malignant diseases or biliary tract diseases was reported in elsewhere (Kurosawa 1986). In the present study, however, the increase of endotoxin level after surgery in patients without either liver cirrhosis or obstructive jaundice was found to be minimal and remained within normal range. On the other hand, the case of hepatectomy showed a moderate and transient increase of the blood endotoxin.

The toxic substances in blood such as endotoxin, bacteria, and many toxic metabolites are mainly metabolized by the reticuloendothelial system. Kupffer cells in the liver are responsible for approximately 90% of reticuloendothelial function, and the spleen, the lung and the bone marrow play a little role (DeNardo et al. 1976). In liver cirrhosis the reticuloendothelial function is thought to be compensated by the spleen instead of the damaged Kupffer cells. However the capacity of splenic reticuloendothelial function does not seem to much work as it is expected. In our clinical study the phagocytic index shown by the injection of chondroitin sulfate iron colloidal particle, which normally has a value of 0.034 ± 0.006 ($n=10$), was significantly reduced to 0.014 ± 0.009 ($n=15$) in the liver cirrhosis group. Hemodynamically, the presence of liver cirrhosis develops the

collateral circulation such as the port-systemic shunt. Accordingly, the patients with liver cirrhosis are easy to develop the systemic endotoxemia spilling over from the portal circulation. In the present study, the preoperative blood values of endotoxin in cirrhotic patients were slightly higher than those in non-cirrhotic patients. Furthermore, the values of endotoxin after surgery markedly increased and continued for a long period. This tendency was more striking in the cirrhotic patients who underwent splenectomy or hepatectomy. It is conceivable that the endotoxemia was produced by a further depression of the reticuloendothelial system induced by the removal of the hepatic functional mass or the splenic phagocytic system. In addition, the postoperative elevation of endotoxin level in patients who had massive blood transfusion during surgery could be caused by the functional exhaustion of the reticuloendothelial system by the excessive phagocytosis of fibrin particles and other activated clotting factors.

In obstructive jaundice the depression of the reticuloendothelial system (Dravis 1976) and the increase of intestinal absorption of endotoxin due to the reduction of bile acids in the gut have been suggested (Kocsar 1969). However, according to the present study, jaundice alone did not produce any increase of endotoxin level. And the reduction of jaundice by PTBD did not make a significant change in the level of endotoxin. However, after the major surgery, a markedly increased and prolonged endotoxin level was observed in jaundiced patients with the preoperative bilirubin level of 5 mg/100 ml or more. In obstructive jaundice, the reticuloendothelial system is thought to be more depressed for a long term even after the reduction of jaundice by PTBD (Dravis 1976), and thereby, increased endotoxin after operation may be spilled over into the systemic circulation.

It is widely known that endotoxin can impair many vital organs so that MOF including gastrointestinal bleeding, respiratory failure, renal failure, DIC, and liver failure is frequently brought about (Wilkinson et al. 1974). The present study showed the increase and continuity of the blood endotoxin level was induced after surgery, especially in liver cirrhosis and obstructive jaundice. And furthermore, the patients who developed postoperative complications showed a notable and persistent high level of endotoxin, which reduced to the normal range concomitantly with the clinical improvement. Based upon these results it may be concluded that a high incidence of MOF after surgery in patients with liver cirrhosis or obstructive jaundice is most likely related to a significant elevation of blood endotoxin level.

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