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The Diagnostic Value of C-Reactive Protein in Bacterial Translocation in Experimental Biliary Obstruction

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A – research concept and design; B – collection and/or assembly of data; C – data analysis and interpretation; D – writing the article; E – critical revision of the article; F – final approval of article; G – other

Abstract

Background. Many experimental studies have verified that obstructive jaundice (OJ) causes bacterial translocation (BT).

Objectives. The aim of this study was to assess to whether C-Reactive Protein (CRP) can be used to detect bacterial translocation induced by biliary obstruction.

Material and Methods. Twenty rats were divided into two groups containing 10 rats each: sham-operated controls and the obstructive jaundice (OJ) group. All procedures were performed aseptically. After an upper midline incision, the common bile duct (CBD) was identified, mobilized, ligated and divided. The sham-operated animals had a similar incision, followed by mobilization of the CBD, without ligation or division. Ten days after the first operation, a second laparotomy was performed. Blood samples were collected for culture and serum CRP analysis. In addition, liver, spleen, and mesenteric lymph node (MLN) specimens were taken for microbiological culture to determine the presence of BT. BT was considered positive if there was any bacterial growth in the MLN, liver, spleen, or blood cultures; a lack of bacterial growth indicated a negative BT.

Results. The OJ group had significantly higher rates of bacterial translocation than the sham-operated group ($p = 0.002$). Mean CRP levels (ng/mL) were 8.7 ± 11.8 and 18.6 ± 17.2 in the sham-operated group and the OJ group respectively. There was no significant difference in mean CRP levels between the two groups ($p = 0.257$). Mean CRP levels were 4.5 ± 4.3 and 24.9 ± 16.4 in the BT (–) and BT (+) groups respectively ($p = 0.003$). A marked increase in CRP levels paralleled an increase in BT.

Conclusions. This study has demonstrated a direct relationship between BT and CRP levels in an experimental OJ model (Adv Clin Exp Med 2014, 23, 2, 197–203).

Key words: C reactive protein, bacterial translocation, obstructive jaundice, cholestasis, animal experimentation.

Patients with jaundice due to extrahepatic biliary obstruction (BO) are still subject to significant morbidity and mortality, despite advances in diagnosis and treatment [1].

Obstructive jaundice (OJ) can be induced in rats by common bile duct (CBD) ligation. CBD ligation has been documented as causing parenchymal cell damage that subsequently leads to liver cirrhosis and hypertension [2]. In rats, marked engorgement of Kupffer cells may hinder sinusoidal blood flow and contribute to the patchy hepatic necrosis seen in this animal model [3, 4].

The main complications of untreated obstructive jaundice include cholangitis, coagulation

defects and liver damage progressing to biliary fibrosis and cirrhosis [2]. Despite advances in pre-operative evaluation and postoperative care, surgical treatment of patients with obstructive jaundice still carries a mortality rate of 10–37% and a major complication rate of up to 60%. Many of the postoperative complications are related to sepsis, renal failure and pulmonary dysfunction [5, 6]. Cardiovascular instability and a predisposition to hypotension and shock have been reported in patients with OJ [7, 8].

Endotoxemia is one of the main complications that can lead to pathophysiological changes in the process of OJ [9–11]. Under normal conditions the

biliary tract is free of indigenous bacteria [12]. It is well known that whenever the biliary tract is obstructed, cholangitis can develop, which can eventually result in septicemia [13]. Several studies have identified elevated intrabiliary pressure as a causative factor in the development of septicemia [14, 15]. In addition, the secretion of IgA in the bile is diminished, which means the ability to bind bacteria and maintain mucosal integrity decreases [16].

The harmful effects of prolonged OJ on the reticuloendothelial system (RES) have been established in experimental and clinical studies [3, 17]. The RES is the primary site for the clearance of bacteria, endotoxin, disrupted cells and cellular debris from circulation, and the liver contains 80–90% of the RES activity in the body. Endotoxemia following disturbed RES function is responsible for elevated postoperative morbidity and mortality [9, 10]. Many experimental studies have verified that prolonged OJ can disarrange the natural ecological balance in the intestinal flora, compromise the host immune system and cause bacterial translocation by deteriorating the intestinal mucosal barrier [18].

The hypothesis that translocation of bacteria and endotoxin from the gastrointestinal tract may initiate or aggravate septic states is increasingly accepted [19]. In this alleged gut hypothesis of sepsis and multiple organ failure, translocated enteric bacteria and endotoxin induce cytokine secretion from tissue macrophages, stimulate neutrophil responses and promote a pro-inflammatory endothelial cell phenotype [20]. Organ damage may be mediated by complement and coagulation system activation, as well as by the products of activated phagocytes and neutrophils, including reactive oxygen intermediates, cytokines and proteases. This theory may clarify why no septic focus is identified in approximately 30% of bacteremic patients dying of sepsis [21]. Furthermore, gut-derived bacteria or endotoxin may induce this sepsis syndrome in the absence of microbiological evidence of infection [22].

A compromised gut barrier function is probably relevant to sepsis in jaundiced patients. The intestine could be a source of systemic endotoxemia; many investigators have reported a high incidence of portal and systemic endotoxemia in jaundice. It has been suggested that gut-derived endotoxins play an important role in the pathophysiology of OJ [23–25]. The gastrointestinal tract has recently been defined as an “undrained abscess” because of its reservoir function for bacteria and endotoxin [26]. However, hosts have developed multiple defense mechanisms that function together to prevent intestinal bacteria and endotoxin from reaching systemic organs and tissues [27]. These include

mechanical and immunobiologic defenses, the stabilizing influences of normal intestinal microflora, as well as a fully functional hepatobiliary system [28]. A loss of intestinal barrier function, which manifests as increased intestinal permeability allowing gut-derived bacteria and endotoxin to cross the mucosal barrier to the mesenteric lymph nodes (MLN) and other distant organ sites, has been documented both clinically and experimentally in a variety of circumstances [28, 29]. In numerous previous studies, using a model of OJ, authors recognized that extrahepatic biliary obstruction promotes the systemic translocation of bacteria from the gastrointestinal tract to visceral tissues [9, 10, 12–14, 18, 22, 24, 25, 27, 28, 30]. It has been reported that endotoxemia is present in 25–85% of OJ [31]. The association between OJ and BT has been reported by several authors [31–33]. The rates of bacterial translocation (BT) observed in OJ are between 20% and 71% [28–33]. The rate of BT is directly proportional to the severity of OJ, and it has been shown that biliary decompression gradually decreases the rate of BT [31, 32].

C-reactive protein (CRP) belongs to a group of acute-phase plasma proteins, initially characterized by their ability to bind to pneumococcal cell wall C-polysaccharide [34]. CRP is a 115-kDa cyclic pentamer acute-phase protein that is a member of the pentraxin family, first identified by Tillett and Francis in 1930 in the serum of patients suffering from pneumococcal pneumonia. Although its functions are still not fully understood, it is known to be a bacterial opsonin, promoting phagocytosis, as well as modulating the complement cascade and platelet activation [35]. Although CRP synthesis by pulmonary [36] and renal [37] cells has been demonstrated, the majority is produced by hepatocytes following stimulation by interleukin 6, with increased expression occurring within four to six hours of an inciting insult [35]. Its production is stimulated mainly by interleukin 6, interleukin 1 β , and tumor necrosis factor α in response to infection or tissue inflammation. CRP has been studied as a screening device for inflammation, as a marker for disease activity and as a diagnostic adjunct. The values of CRP may reflect the severity of inflammation or tissue injury [38], and it is a potential marker of the presence of infection and severity of sepsis [39, 40]. An elevated blood CRP concentration is thought to be highly suggestive of bacterial infection, though other non-infectious conditions may also elevate CRP [41]. It is also a marker of ischemia, especially in patients with coronary artery, cerebrovascular, or peripheral vascular disease. CRP levels are also used as a prognostic indicator for some revascularization procedures [42]. CRP levels are raised and serve as

a predictor in patients who have progressed to severe pancreatitis [43]. It has been reported CRP can be used in the evaluation of treatment effectiveness [44]. La Greca et al. found CRP levels significantly higher in patients with cancer such as pancreatic cancer, gall bladder cancer and intrahepatic cholangiocarcinoma, probably due to an intensive inflammatory response to the tumor [45]. Raised serum C-reactive protein concentration at the time of presentation of advanced pancreatic cancer carries a poor prognosis independent of biliary tract obstruction [46].

No previous studies have been aimed at evaluating the diagnostic value of CRP in bacterial translocation in experimental obstructive jaundice. The authors of the current study tested the hypothesis that CRP levels may be a useful marker of BT in experimental biliary obstruction.

Material and Methods

Animals

Twenty albino Wistar rats weighting between 200 and 250 g were included in this study. The rats were maintained in standardized conditions in terms of food, water, light, and temperature. All the animals were fed standard rat chow and water ad libitum, and were given only water for 14 hours before the surgery. The Ethics Committee of Suleyman Demirel University Medical School approved the experimental procedures used in this study. The animals were obtained from the breeding unit of the Suleyman Demirel University School of Medicine and all of the guiding principles in the care and use of laboratory animals were strictly adhered to throughout the entire study.

Experimental Design

The animals were divided into two groups of ten rats. The first group served as the sham-operated controls, and underwent laparotomies in which the CBD was manipulated but not ligated or divided. The second group, which served as the OJ group, underwent laparotomies in which the CBD was ligated and divided.

Surgical Technique

All the procedures were performed aseptically. The rats were anesthetized using intramuscular injections of 25 mg/kg ketamine hydrochloride (Ketalar®, Parke-Davis, Eczacıbaşı, Istanbul, Turkey) and 10 mg/kg xylazine (Rompun®, Bayer, Leverkusen, Germany). After shaving the abdomen and

preparing the site with 10% povidone-iodine solution, the abdomen was opened through a small upper midline incision. The CBD was identified, mobilized, doubly ligated using 4-0 silk and divided. The sham-operated animals had a similar incision followed by mobilization of the CBD without ligation or division. All abdominal incisions were closed in two layers using 3-0 polyglactine (Vicryl®; Ethicon, Woluwe, Belgium) and 4-0 polypropylene (Prolene®; Ethicon, Woluwe, Belgium).

Ten days after the first operation, a second laparotomy was performed. Liver, spleen, MLN and portal blood samples were taken for microbiological culture. After completing the experimental procedure the animals were sacrificed.

Bacterial Translocation

Portal blood samples of 1–2 mL were cultured aerobically using BacTec Peds blood culture bottles (Becton, Dickinson and Company, USA) under sterile conditions. The blood cultures were continuously monitored for ten days. The growing microorganisms were subcultured on blood agar and eosin methylene blue agar. The rest of the blood samples were centrifuged at 3000 rpm for 10 min, and the resultant sera were separated for CRP assay.

The MLN, spleen and liver samples were homogenized with sterile sand in 2 mL of distilled water, in separate Petri dishes. After homogenization, the tissue residues were centrifuged at 1000 rpm for 2 min. Dilutions of 10^1 , 10^2 , and 10^3 were then made using 100 μ L of supernatant. A portion (100 μ L) of each diluted specimen was then inoculated on blood agar, eosin methylene blue agar and chocolate agar and incubated for 24–48 h at 35°C under aerobic conditions.

Following incubation, the bacterial colonies on the blood agar and chocolate agar were counted, and mean values for the 100 μ L samples were calculated. Each calculation took into account the starting volume of the homogenate and dilution ratios. The values were expressed as colony forming units (cfu) of the bacteria per 1 g of tissue (wet weight). The microorganisms were also identified using conventional tests and the Becton Dickinson identification system.

BT was considered positive in case of any bacterial growth in MLN, liver, spleen or blood cultures, whereas a lack of bacterial growth indicated a negative BT.

The rat CRP enzyme-linked immunosorbent assay (ELISA) is based on a solid phase ELISA. The rat CRP of serum was performed using a commercial kit (Life Diagnostics, Inc., Westchester, PA, USA), according to the manufacturer's instructions.

A standard curve was constructed by plotting the mean absorbance obtained from each reference standard against its concentration in ng/mL on linear graph paper, with absorbance values on the vertical or Y-axis, and concentrations on the horizontal or X-axis.

Statistical Analysis

All the statistical analyses were carried out using SPSS for Windows (SPSS Inc., version 13.0, Chicago, IL, USA). The results were evaluated using the Mann Whitney U-test. All values were expressed as mean \pm standard deviation. Differences were considered significant when P was less than 0.05.

Results

There had been no death in either group by the 10th day. The number of positive cultures for all the samples in each group is shown in Table 1. One of the ten subjects in the sham-operated group (10%) had bacterial growth in their MLN and spleen tissue cultures, but no bacterial growth was noted in either liver tissue or blood cultures.

In the obstructive jaundice group, bacterial growth was found in eight of the ten MLN cultures (80%), eight of the ten liver tissue cultures (80%), eight of the ten spleen tissue cultures (80%), and seven of the ten blood cultures (70%).

The frequency of positive cultures was significantly higher in the OJ group than in the control group. P values for the MLN, liver, spleen, and blood cultures were $p = 0.002$, $p < 0.001$, $p = 0.002$ and $p = 0.001$ respectively. The OJ group had also significantly higher rates of bacterial translocation than the sham-operated group ($p = 0.002$).

The predominant pathogens obtained from the MLN, liver, spleen and blood were *Escherichia coli* (*E. coli*), *Enterobacter cloacae*, *Enterococcus faecium* and *Staphylococcus aureus*. The most common microorganism found in all cultures was *E.coli* (Table 2).

Mean CRP levels (ng/mL) were 8.7 ± 11.8 and 18.6 ± 17.2 in the sham-operated group and the OJ group respectively. There was no significant difference in mean CRP levels between the two groups ($p = 0.257$).

When the mean CRP levels were evaluated according to the positiveness of BT, mean CRP levels were 4.5 ± 4.3 and 24.9 ± 16.4 in the BT (–) and

Table 1. The number of positive cultures for each group in all samples

Groups	MLN	Liver	Spleen	Blood	Total BT
Sham-operated control (n = 10)	1	0	1	0	1
Obstructive jaundice (n = 10)	8	8	8	7	8
Total	9	8	9	7	9

BT (+) groups respectively. There was a significant difference in the mean CRP levels between BT (–) and BT (+) groups ($p = 0.003$). A marked increase in CRP levels paralleled an increase in bacterial growth and BT.

Discussion

The present study clearly showed that obstructive jaundice caused bacterial translocation. The study also demonstrated that OJ can be induced in the rat by common bile duct ligation. This model was reliable, with no procedure-related mortality, suggesting that ligation of the common bile duct for ten days is non-lethal but promotes BT.

In the present study, BT was demonstrated in cultures of blood, MLN, spleen and liver samples obtained from animals with obstructive jaundice.

Increased intestinal permeability and BT have

Table 2. Types of bacteria grown in cultures by subject group

Culture type	Sham operation group	OJ group
MLN	<i>Escherichia coli</i>	<i>Escherichia coli</i> <i>Enterobacter cloacae</i> <i>Enterococcus faecium</i> <i>Staphylococcus aureus</i>
Liver	no bacterial growth	<i>Escherichia coli</i> <i>Enterobacter cloacae</i> <i>Enterococcus faecium</i> <i>Staphylococcus aureus</i>
Spleen	<i>Escherichia coli</i>	<i>Escherichia coli</i> <i>Enterobacter cloacae</i> <i>Enterococcus faecium</i> <i>Staphylococcus aureus</i>
Blood	no bacterial growth	<i>Escherichia coli</i> <i>Enterobacter cloacae</i> <i>Enterococcus faecium</i>

been demonstrated following both experimental jaundice and jaundiced patients [18, 28]. Deitch has proposed three factors that promote this process: (i) disruption of the indigenous gut microecology; (ii) physical injury of the gut mucosa; and (iii) impairment of host immunity [47]. Steffen and Berg demonstrated a correlation between the incidence of bacterial translocation to mesenteric lymph nodes and cecal bacterial overgrowth in mice [48]. Intestinal anaerobic bacteria outnumber aerobic and facultative bacteria by 100 : 1 or 1000 : 1, but rarely seem to be translocated [47]. Anaerobes have been thought to control the colonization and concomitant translocation of facultative bacteria. Thus, a disruption of the balance in the enteric microflora seems to occur in OJ [49]. The current study demonstrated a significant increase in the incidence of BT in the MLN, liver, spleen and blood in jaundiced rats.

The most commonly encountered pathogens in the MLN, liver, spleen and blood were *E. coli*, *Enterobacter cloacae*, *Enterococcus faecium* and *Staphylococcus aureus*. These pathogens were also determined to be the most common in various other studies [42, 50]. One limitation of the present study is the exclusion of an anaerobic culture, which should also be examined. On the other hand, anaerobes are isolated in only a small percentage of infected bile [34].

Although elevation of acute phase reactant levels, such as CRP, is a non-specific host response to infection, inflammation and tissue injury, measuring alterations in these levels can be clinically useful when an infection or inflammatory response is suspected [44–47, 51, 53]. In the present study, CRP levels did not significantly differ between the sham-operated group and the OJ group. This may reflect the non-specific nature of the response of CRP to inflammation and infection, which impairs its selectivity for OJ. The observed increase in CRP levels may have been due to a systemic inflammatory response to surgery. A weakness of the experimental design could be the lack of an “anesthesia control group”. But when the mean CRP levels were evaluated according to positiveness of BT, there was a significant difference in mean CRP levels between the BT (–) and BT (+) groups ($p = 0.003$). A marked increase in CRP levels paralleled an increase in bacterial growth and BT.

Results from several studies suggest that surgery also increases the likelihood of bacterial translocation [53, 54]. In this study, one of the ten subjects in the sham-operated group (10%) had bacterial growth in their MLN and spleen tissue cultures, but no bacterial growth was shown in either liver tissue or blood cultures. Although surgery may have contributed to bacterial translocation in the present study, the rate of bacterial translocation in the OJ group was significantly higher than in the sham-operated control group ($p = 0.002$).

This study demonstrated a direct relationship between the BT and CRP levels in an experimental model of obstructive jaundice. Although such a relationship has not been previously established in this model, prior results suggest possible mechanisms. As mentioned previously, endotoxin is a potent trigger of the mediator cascade and may have an important role in inducing mediators of the acute phase reaction [55]. Endotoxin also can cause systemic inflammatory response syndrome, multiple organ failure, septic shock and even non-septic shock [56, 57]. The luminal flow of bile salts has antibacterial effects and a direct detergent effect on endotoxins, and it has been suggested that the increased absorption of endotoxin in OJ may be associated with an absence of bile salts in the small intestine [28, 58]. Therefore, with the absence of bile, translocation of endotoxins along with bacteria in cases of OJ may cause a parallel increase in CRP levels. Furthermore, high concentrations of serum CRP are closely related to a high risk of organ failure and death [59].

The authors consider CRP estimation a direct semi-quantitative, simple, sensitive and inexpensive measure of acute phase reaction and, due to its kinetics, provides adequate information regarding the stage of bacterial infections and BT.

In conclusion, CRP levels do not appear to be of value in distinguishing biliary obstruction. However, serum CRP levels may be useful for predicting and determining the severity of bacterial translocation in cases of obstructive jaundice. The ability to detect changes in CRP levels this early is clinically useful, as it provides an opportunity to use this information in patient management.

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