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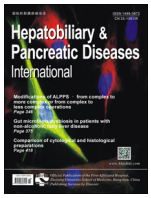

Review Article

Pathophysiological consequences of obstructive jaundice and perioperative management

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ABSTRACT

Background: Obstructive jaundice is a common problem in daily clinical practice. Understanding completely the pathophysiological changes in obstructive jaundice remains a challenge for planning current and future management.

Data sources: A PubMed was searched for relevant articles published up to August 2016. The effect of obstructive jaundice on proinflammatory cytokines, coagulation status, hemodynamics and organ functions were evaluated.

Results: The effects of obstructive jaundice included biliary tree, the hepatic cell and liver function as well as systemic complications. The lack of bile in the gut, the disruption of the intestinal mucosal barrier, the increased absorption of endotoxin and the subsequent endotoxemia cause proinflammatory cytokine production (TNF-α, IL-6). Bilirubin induces systemic inflammatory response syndrome which may lead to multiple organ dysfunction syndrome. The principal clinical manifestations include hemodynamic instability and acute renal failure, cardiovascular suppression, immune compromise, coagulation disorders, nutritional impairment, and wound healing defect. The proper management includes full replacement of water and electrolyte deficiency, prophylactic antibiotics, lactulose, vitamin K and fresh frozen plasma, albumin and dopamine. The preoperative biliary drainage has not been indicated in overall, but only in a few selected cases.

Conclusion: The perioperative management is an essential measure in improving the outcome after the appropriate surgical operation in jaundiced patients especially those with malignancy.

Introduction

Historical aspects show that jaundice is one of the earliest diseases known even before the Hippocrates time. It is derived from the French word jaune, which means yellow discoloration. The concept of obstructive jaundice came up in 1935 by Whipple [1].

Obstructive jaundice caused by ligation of the common bile duct is the current useful experimental model for detailed cell biology study in molecular level. It has contributed to the better knowledge of the exact pathophysiological events and the assessment of the effect of various therapeutic factors.

Obstructive jaundice induces various pathophysiological consequences including local effects on the biliary tree and systemic manifestations [2]. Therefore, patients with jaundice are at high risk to develop liver dysfunction, renal failure, cardiovascular suppression, nutritional fail, bleeding trend, immune compromise and infections, wound incision complications and increased morbidity and mortality. The complete understanding of pathophysiology in jaundiced patients necessitates the application of the optimal preventive measures perioperatively in order to improve the outcome [3].

Local effects on the biliary tree

The normal pressure into the biliary tree fluctuates between 5 and 10 cm H_2O. Anything interfering with bile's normal flow causes pressure elevation. The intraluminal pressure can reach up to 30 cm H_2O in complete obstruction; the bile excretion from the hepatic cell is interrupted when the pressure exceeds 10–15 cm H_2O [4].

Cholestasis favors microbe growing and proliferation within the bile, which otherwise, in normal condition, is sterile by bacteria. The cholangitis is ascending from duodenum microbial flora. As pressure is increased into the biliary tree, the barrier from the

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strong conjunction between the hepatic cell and bile microduct is impaired resulting in increased permeability and bile backflow within hepatic sinusoids; hence, this backflow within the blood allows the entrance of microbes and their degradation products into systemic circulation. Cholangitis mainly happens in acute obstruction. The increased biliary pressure pushes the bacterial infection into the biliary canaliculi, hepatic veins, and perihepatic lymphatics causing bacteremia [5]. The onset of acute cholangitis involves both increased bacteria into the biliary tree and elevated intraductal pressure. Thus a translocation of bacteria and endotoxin into the vascular system occurs (cholangio-venous reflux). The increased intraductal pressure in acute cholangitis tends to make the ductules more permeable to the translocation of bacteria and toxins, which leads to severe infection and sepsis [6]. Furthermore, the backflow causes inflammatory infiltration of portal sinusoids by polymorphonuclear neutrophile leucocytes and increased fibrin deposition [7].

In a case of chronic partial obstruction, the gradual increase of biliary pressure induces proximal dilatation of both intrahepatic and extrahepatic bile ducts as well as liver dilatation (cholestatic liver) [4,7,8]. The dilatation degree depends on the cause and duration of the obstruction and the compliance of the liver and biliary tree. In recurrent inflammation, this dilatation may be absent due to cumulative fibrosis. The latter affects nevertheless also the portal sinusoids causing initially reversible portal hypertension, provided the restoration of bile flow by removing or bypassing the obstruction cause; later if the obstruction consists then the progressive biliary cirrhosis and severe hepatocellular damage are unavoidable [9].

Liver effects

The raised pressure in the biliary tree can restrict gradually the production of bile by the hepatic cell. However, the risk of biliary lithogenesis is low, because of the observed higher reduction in secretion of cholesterol and phospholipids than those of bile salts. The latter, as known, ensures the cholesterol solubility into the bile. Sequentially, when the obstruction is repaired and the intraluminal pressure is normalized, then inversely, the restoration of cholesterol and phospholipids secretion is faster than those of bile salts which favors lithogenesis; thus, increasing the risk of cholesterol crystal segmentation and micro gallstones formation. The latter has resulted in early stent obstruction, which was inserted for bile duct drainage and decompression in the management of obstructive jaundice [7,10].

Cholestasis affects hepatic blood flow which explains the worsened liver dysfunction. Apart from the secretory capacity, obstructive jaundice influences significantly the metabolic and synthetic capacity of the liver. The substances normally excreted by the liver, in obstruction, a backflow into the systemic circulation causing major toxicity. The increased bile salts inhibit hepatic cytochrome P450 and reduction of oxidative or aerobic metabolism, which increase the oxidative stress and hepatic apoptosis. The inhibited hepatic cytochrome P450 and its dependent, microsomal mixed function oxidase (MFO), affects the metabolism of drugs and other extrinsic or intrinsic substances [10]. The reduced synthetic capacity results in low levels of albumin, coagulation factors and immunoglobulins such as IgA. Nutritional assessment has shown a high incidence of protein-calorie malnutrition [11]. Also, it has been noted a reduction in the expression of major histocompatibility complex (MHC) antigen and increase in proinflammatory cytokine (TNF-α, IL-6) levels [10].

It has been proposed the protection of acute cholestatic liver injury via inhibition of the apoptosis pathway by microRNA-29 (miR-29), which reduces fibrosis and cirrhosis [12]. The excessive hepatocyte apoptosis and bile lakes before and after bile duct decompression have been evaluated [13].

The decrease of hepatic peroxisome proliferator-activated receptor-γ (PPAR-γ) increases the sensitivity to endotoxin [14]. PPAR-γ belongs to the nuclear receptor family that regulates the adipocyte differentiation, lipid metabolism, glucose homeostasis and cell proliferation. Its reduction increases the proinflammatory cytokines i.e. TNF-α, IL-6 and liver injury. The serum sialic acid, a marker of inflammation and oxidative stress, is increased in obstructive jaundice [15]. Liver elasticity, which evaluates the severity of liver fibrosis, is increased in patients with obstructive jaundice [16].

The cholestasis affects the phagocytotic activity of Kupffer cells. Biliary decompression restores the function of Kupffer cells [17,18].

Gut and intestinal barrier effects

The blockage of bile salts into the intestinal tract induces the proliferation of the normal microbial flora, dysfunction of the intestinal mucosal barrier, bacterial translocation, and ultimately increases endotoxin absorption [7].

The intestinal barrier failure including immunological, biological and mechanical disruption leads to increased intestinal permeability, [19] which plays a pivotal role in the development of septic and renal complications. The mechanism of intestinal barrier dysfunction and hyper-permeability has been attributed to the decreased intestinal epithelial cell proliferation and altered expression of tight junction proteins [20]. It has been found that the gut regulatory peptides bombesin and neurotensin can prevent this alteration and reduce endotoxemia [21]. The modulation of gut barrier function by probiotics has been proposed [22].

Endotoxin

Endotoxin, also known as lipopolysaccharide (LPS), derived from the wall destruction of gram negative bacteria. Under normal circumstances, the small amounts of endotoxin generated from the gut are transferred via the portal vein to the liver, where it is inactivated by the hepatic reticuloendothelial system. The increased absorption of gut origin endotoxin in combination with liver dysfunction, both seen in obstructive jaundice, lead to systemic inflammatory response syndrome (SIRS), which may cause multiple organ dysfunction syndrome (MODS). These systemic effects are firstly and mainly manifested by hemodynamic instability and acute renal failure [23–27].

Hemodynamic effects

Liver hemodynamic assessment by Color Doppler flow imaging indicated an increase in hepatic artery flow and a decrease in the portal vein flow [28]. The circulating volume of blood in the liver is an important factor, which affects liver functions; thus, liver hemodynamics is a predictor of hepatic function restoration after an operation. The overall hemodynamic effects have been attributed to the compromised cardiac function (contractility, elasticity, low cardiac output) as well as in the decreased peripheral resistances, both predisposing to shock event postoperatively. It has been described in detail the cardiac depression namely jaundice heart [3]. In addition to cardiac function, another contributing factor to hemodynamic instability is the loss of extracellular water and electrolytes due to the effect of an atrial natriuretic peptide (ANP). ANP is released by the heart atriums causing excessive sodium and urine output as well as peripheral vasodilatation. The reduced cardiac output may lead to atrial dilatation and increase of this peptide ANP aiming to offset the action of hormones i.e.