

Review Article

Anesthesia for Patients with Obstructive Jaundice

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ABSTRACT

Aim of review: Obstructive jaundice is associated with high perioperative morbidity and mortality due to diverse pathophysiological derangements. Proper preoperative evaluation and preparation, and optimal perioperative anesthetic management contribute significantly to a favorable outcome for patients with obstructive jaundice during the perioperative period. In this review, we attempt to summarize the pathophysiological changes induced by obstructive jaundice and update the anesthetic management of jaundiced patients.

Methods: Review of recently published literature (from January, 1960 to December, 2017) related to obstructive jaundice and anesthetic management. Keywords searched include “obstructive jaundice” or “cholestasis”, “anesthetic management”, “pathophysiology” or “physiopathology” or “pathology and physiology”.

Recent findings: Obstructive jaundice causes a series of pathophysiological changes, including changes in blood biochemistry and metabolism, coagulation, infection, liver injury, renal dysfunction, cardiovascular instability, malnutrition, stress ulcer, bacterial translocation, immunosuppression and other adverse events, all of which may increase the mortality and morbidity during the perioperative period. The alterations in pharmacological properties of many narcotic drugs caused by obstructive jaundice vary widely. And the requirements of many anesthesia-related drugs, such as rocuronium, desflurane and etomidate, are reduced in patients with obstructive jaundice.

Conclusion: Pathophysiological changes associated with obstructive jaundice need to be improved preoperatively. Anesthesiologists should be aware of the importance of rational use of narcotic drugs in patients with obstructive jaundice during operation. Multidisciplinary collaboration is required for the treatment of such patients perioperatively. (Funded by the National Natural Science Foundation of China.)

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Citation: Yue Long, Weidong Mi, Weifeng Yu. Anesthesia for Patients with Obstructive Jaundice. *J Anesth Perioper Med* 2018;5:149-60.

doi: 10.24015/JAPM.2018.0058

Obstructive jaundice is a common clinical pathophysiological condition characterized by increased serum bilirubin level because of bile flow obstruction due to blockage of the large bile ducts. The major causes of obstructive jaundice include biliary calculi or stenosis of the bile ducts either secondary to biliary calculi or as a complication of cholecystectomy, and periampullary malignant tumors, however, in patients with cholestasis, other sources of obstruction should also be considered (Table 1) (1, 2).

Surgical resection is generally considered the main effective treatment for obstructive jaundice.

Patients with obstructive jaundice are inclined to develop nutritional deficits, hypotensive shock, acute renal failure, sepsis, and multi-organ failure during the perioperative period (3). The perioperative morbidity and mortality in patients with obstructive jaundice are higher than those in non-jaundiced patients (4). Earlier studies have shown that the perioperative mortality in patients with obstructive jaundice is about

16%-18%, and the incidence of acute renal failure in perioperative period is 8% - 10% in patients with obstructive jaundice and the eventual mortality is 70%-80% in those who develop it (3). Adverse events such as coagulopathy, extracellular water depletion (5), defective vascular reactivity (6), subclinical myocardial dysfunction (7), systemic endotoxemia (8), and exaggerated release of proinflammatory cytokines in response to endotoxin challenge (9) may contribute to the increased mortality and morbidity, which may impose a considerable challenge upon anesthesiologists, surgeons, and intensive care teams.

Pathophysiology of Obstructive Jaundice

Alterations in Blood Biochemistry

Blood biochemical indexes, including serum total bilirubin (STB), serum conjugated bilirubin (SCB), bile acids, cholesterol, alkaline phosphatase (ALP), γ -glutamyl transpeptidase (γ -GT), alanine aminotransferase (ALT), aspartate aminotransferase (AST), lipoprotein-x (LP-X) and 5'-nucleotidase, are increased significantly in jaundiced patients as compared with those in non-jaundiced patients. ALP is a reliable indicator of cholestasis. ALT is an enzyme from the cytoplasm of the liver, its increase is not apparent in the early stages of biliary obstruction, but it can be significantly increased when the synthesis of liver cell was damaged. AST is an organ-nonspecific enzyme located in many tissues of the human body where it catalyzes reversible reaction of transamination. The serum AST rises obviously in patients with biliary obstruction, especially acute infections is present.

The Change of Metabolism

In normal physiological conditions, serum conjugated bilirubin is excreted into the intestine via the bile duct, where its glucuronic acid base is removed by β -glucuronidase of intestinal bacteria and then reduced to urobilinogen in the terminal ileum and colon. Most urobilinogen is oxidized to urobilin and expelled from the feces in the form of fecal urobilin. A small proportion of urobilinogen is reabsorbed in the colon and back to the liver via the portal system, and is discharged through the bile duct after metabolism and transformation in the liver, which is known as the en-

terohepatic circulation of bilirubin. Bilirubin cannot be discharged or only some of it is discharged into the intestines when biliary obstruction occurs, thus affecting the enterohepatic circulation of serum conjugated bilirubin. As a result, urobilinogen and bilirubinuria disappear or are greatly reduced in the intestines, as typically represented by a negative result of urobilinogen test and clay-colored stool. Prolonged biliary obstruction may impair the hepatocellular function of absorbing, carrying and esterifying unconjugated bilirubin. When the esterification process of β -glucuronidase in the tissue is impaired, serum unconjugated bilirubin is increased.

There are 15 bile acids in human bile, including cholic acid, chenodeoxycholic acid, deoxycholic acid, a small amount of lithocholic acid, and trace amounts of ursodeoxycholic acid. In patients with biliary obstruction, bile acids cannot be completely discharged into the intestines due to obstruction of the enterohepatic circulation. As a result, bile flows back to the blood, causing a marked increase in serum bile acids. These bile acids that cannot enter the intestines may induce bacterial translocation, resulting in endotoxemiopathophysiological disorders.

Obstructive jaundice can induce fat-soluble vitamin K malabsorption and affect the synthesis of coagulation factors VII, IX and X, thus reducing the level of prothrombin in the liver and increasing the risk of bleeding. We also found that lysophosphatidylcholine (LPC) was increased and phosphatidylcholine (PC) was decreased in a bile duct ligation rat model, indicating the presence of abnormal phospholipid metabolism and an imbalanced oxidative environment under the condition of bile obstruction. In addition, increased kynurenine (Kyn) may be associated with the development of hypotension, renal failure and immunosuppression in patients with obstructive jaundice (10).

Hepatic Pathophysiology

A severe liver injury is one of the main consequences of obstructive jaundice (11). Obstructive jaundice-related hepatic injury includes hepatocellular necrosis and apoptosis, bile duct epithelial cell proliferation, and liver fibrosis (12). It was reported that endotoxemia, inflammatory cell infiltration, microvascular perfusion failure and Toll-

like receptor (TLR) activation were involved in the pathogenesis of obstructive jaundice-induced liver injury, though the concrete mechanisms remain largely unknown (13). Inflammatory factors, such as tumor necrosis factor- α (TNF- α), interleukin-6 (IL-6), and interleukin-1 β (IL-1 β), play significant roles in obstructive jaundice-induced liver injury, and are involved in the high incidence of perioperative complications and high mortality rates (11, 14). Endotoxemia occurs frequently in patients with jaundice. LPS was found capable of inducing the release of proinflammatory cytokines, including TNF- α and IL-6 (15).

Renal Pathophysiology

Acute renal failure is a serious consequence of obstructive jaundice, with an incidence of 6%-18% (16), which further increases the incidence of postoperative morbidity and mortality (17). Hypotension, sepsis, depletion of extracellular fluid, myocardial dysfunction, hypoproteinemia, hyponatremia, and hypokalemia have proven to be closely related to the development of kidney disease in patients with obstructive jaundice (5, 7).

The mechanism underlying jaundice-associated renal failure has not been fully expounded and needs to be further clarified. Likely explanations are outlined below.

The incidence of postoperative acute renal failure in patients with obstructive jaundice appears to be directly related to the degree of jaundice. It was reported that the incidence of renal failure in patients with obstructive jaundice was significantly higher than that observed in non-jaundiced patients (18), and the postoperative creatinine clearance rate was decreased markedly compared with that in the control group (19).

At present, most scholars believe that damage to the normal function of the circulatory system and decompensation of the circulatory system may be the main cause of renal failure, especially under the condition of surgical and narcotic stress, bleeding, endotoxin and other adverse events. Cardiovascular function in jaundiced patients is depressed and responsiveness to vasoactive substances such as α , β -adrenoreceptor and angiotensin II stimulation is blunted (20). These factors can reduce the blood flow rate and then damage the renal function.

Renal failure in jaundiced patients is concerned

Table 1. Benign and Malignant Causes of Obstructive Jaundice.

Benign Causes of Obstructive Jaundice	
Bile duct calculus or gallstones (Mirizzi' syndrome)	
Pancreatic pseudocyst	
Biliary stricture (Caused by inflammation or surgery)	
Hemobilia	
Liver flukes or Worm	
Malignant Causes of Obstructive Jaundice	
Cholangiocarcinoma	
Gallbladder cancer	
Pancreatic cancer	
Ampullary cancer	
Hepatocellular carcinoma with tumor thrombus	
Lymphoma	
Metastatic disease	

with the existence of bacterial endotoxins in the peripheral blood, and the absence of bile salts facilitates enteric endotoxin absorption from the intestines (21). Endotoxins entering the systemic circulation may then cause renal vasoconstriction.

Blood loss and fluid shifts may be another major factor underlying renal dysfunction in obstructive jaundice. It was reported that a decreased intravascular volume may increase the incidence of renal failure in jaundiced patients, especially when they received various invasive procedures (22). Correction of volume deficits in obstructive jaundice could increase renal blood flow and urinary excretion of hepatic metabolites, and reduce circulating concentrations of toxic substances (23). In addition, the preoperative use of nephrotoxic drugs such as aminoglycoside antibiotics, an exacerbation of lipid peroxidation (24), the decreased expression of protective apoptosis-related protein and increased expression of pro-apoptotic protein may exacerbate kidney damage.

Cardiovascular Effects

Change in Cardiac Function

Cardiovascular instability due to defects in myocardial performance is thought to play an important role in the physiopathology of multi-organ

dysfunction syndrome in obstructive jaundice (25, 26). It was reported that cholemia may impair the left ventricular performance in a dog model (25), and this hepatic cardiomyopathy is termed as "jaundiced heart", which is ascribed to altered beta-adrenergic receptor signaling (27), membrane fluidity, and down-regulation of cardiac beta-adrenoceptor density and affinity (28).

Cardiomyocytes, myocardial conduction and contraction are influenced in obstructive jaundice. Bile acids can exert a negative inotropic effect manifested as a decrease in active tension, the maximum rate of tension activation, and the maximum rate of tension relaxation (29). There is also evidence that biliverdin can induce atropine bradycardia and hypotension in dogs (30).

It was reported that addition of the serum from cholestatic rats to cultured myocardial cells reduced the beating rate, caused an early cessation of beating and increased the production of lactate in the media (31). Bradycardia was also observed in rats with obstructive jaundice (32).

Vascular Hyporeactivity

Vascular hyporeactivity is one of the main possible mechanisms for the high incidence of complication and increased mortality rate in obstructive jaundice (6, 33). Experimental studies in animals and humans have clearly demonstrated that the reactivity to endogenous or exogenous vasoactive substances such as angiotensin II, norepinephrine and other sympathomimetic was damaged in obstructive jaundice (33). They then conclude that the impaired responsiveness to pressor substances is not a crucial factor for systemic hypotension in rats with cholestasis induced by bile duct ligation (34). Our study also found that baroreflex sensitivity in patients with obstructive jaundice was impaired (35), and the systolic function of the thoracic aorta in rats with obstructive jaundice was significantly decreased, and the diastolic function was relatively strengthened as compared with the sham control rats (36). In brief, the peripheral vascular resistance is decreased, blood pressure is declined, and the blood vessels become insensitive to endogenous and exogenous stressors in obstructive jaundice.

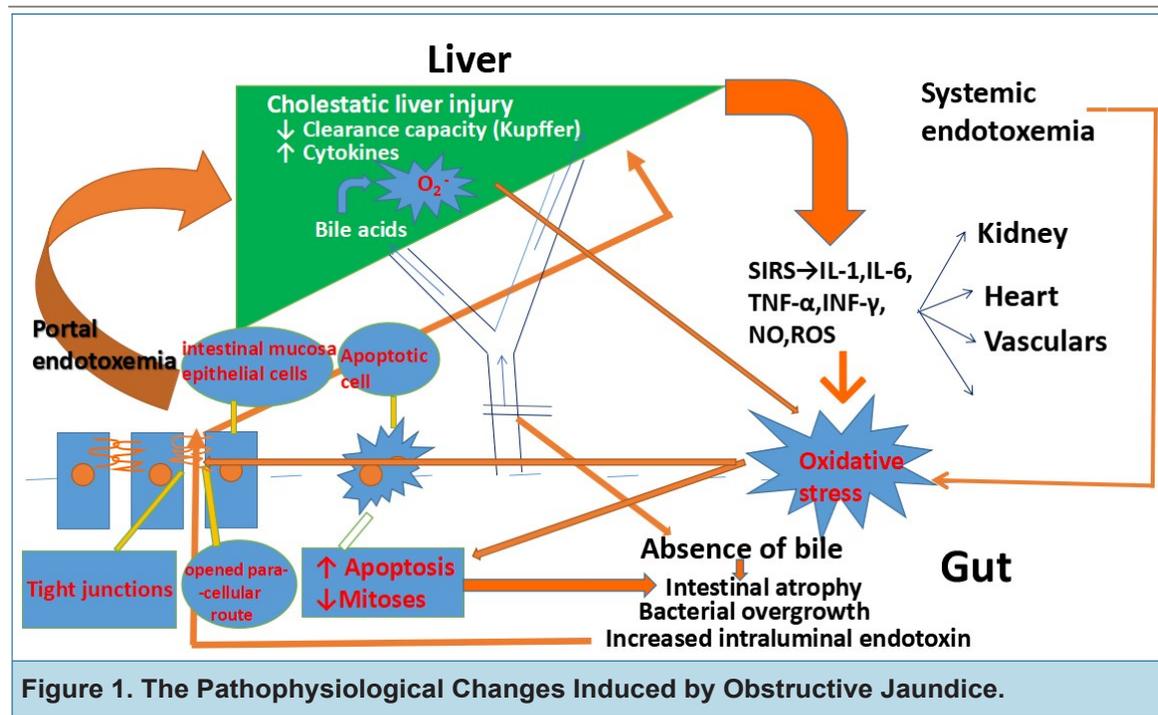
Many factors, including sodium taurocholate (37), endotoxin (38), increased endogenous opioid peptides (39), and prostaglandin (40), are

thought to play roles in vascular hyporeactivity induced by cholestasis. There is also evidence that nitric oxide (NO) works in cholestasis-associated vascular hyporesponsiveness (41). Alon et al. found that hypercholesterolemia in the choledococaval anastomosis (CDCA) canine model may decrease the responsiveness to vasoactive substances (42). In vitro experiments also showed that many types of bile acids (both binding and secondary bile acids) could decrease the vascular reactivity of arteries (43) and various types of veins such as the portal vein, vas deferens vein and hindlimb vein (44). In addition, substantial liver damage caused by obstructive jaundice may also lead to the occurrence of low vascular reactivity (45). The accumulation of some vasodilating substances like bradykinin, substance P, vasoactive intestinal peptide (VIP), glucagon, prostacyclin, atrial natriuretic peptide and kynurenine found by our group may also be involved in the development of hyporesponsiveness. However, it is still necessary to further clarify whether there are specific substances or factors that are involved in the occurrence of vascular hypotension.

Volume Depletion

Animal experiments showed that rabbit plasma and extracellular fluid volume were decreased after ligation of the common bile duct (46). Padillo et al. used bioelectrical impedance techniques to measure the volume and distribution of body fluid in jaundiced and non-jaundiced patients and found that there was no significant difference in the intracellular fluid volume between the two groups, but the total amount of liquid and the extracellular fluid volume were significantly reduced in patients with obstructive jaundice as compared with those in non-jaundiced patients, which is irrelevant to whether the cause of obstructive jaundice is benign or vicious (47).

Animal and clinical studies showed that endocrine hormones, such as aldosterone, renin and antidiuretic hormone, are known to be closely related to the regulation of water and salt metabolism. These hormones significantly increased, suggesting that the blood volume was decreased (48). It was reported that the enhance risk of adverse cardiovascular outcomes could be ameliorated by fluid infusion prior to surgery, sug-



gesting an exaggerated hypotensive response to volume depletion in obstructive jaundice (49).

Blood volume reduction may be related to the following factors.

1. Thirst loss and decreased intake of water (48). Scientists conclude that thirst loss may be associated with abnormalities in the hypothalamus-related nerve regions (50), and increased atrial natriuretic peptide (ANP) may be an important cause of decreased intake of water in obstructive jaundice (51).

2. Increased secretion of ANP and brain natriuretic peptide (BNP) (7). Both ANP and BNP have potent natriuretic and diuretic effects, and inhibit the function of the animal drinking water via the central nervous system (CNS). The cardiac function injury caused by obstructive jaundice may be the main reason for increased ANP and BNP.

3. The diuretic and natriuretic effects of bile salt (52).

Knowing that obstructive jaundice can decrease the effective circulatory blood volume, researchers have attempted to improve the compensatory capacity of the circulatory system, renal perfusion and renal function by preoperative fluid therapy. Williams et al. found that preoper-

ative blood transfusion could reduce the perioperative mortality (49). The surgical mortality was 13.6% in 195 patients, only 32% of which received preoperative transfusions. When 58% of the 155 patients have received preoperative transfusions, the mortality significantly lowered to 7.1%. There are controversies over whether mannitol has a protective effect against renal function damage. Some animal and clinical studies suggest that mannitol can protect renal function (53). However, Gubern et al. argued that mannitol was unable to prevent renal failure in jaundiced patients; rather the diuretic action of mannitol had a potential adverse effect (54). A randomized controlled study showed that administration of dopamine alone or in combination with mannitol or furosemide did not confer more renal protection, while the maintenance of a sufficient perioperative blood volume was the key to the protection of renal function (55). Parks et al. found that, with abortive preoperative resuscitation and maintenance of fluid and electrolyte balance, the occurrence of postoperative renal dysfunction in jaundiced patients was not as high as that in some previous studies and was unaltered by administration of perioperative

low dosage dopamine (56). However there is also clinical evidence that preoperative fluid administration expanded the extracellular water compartment but failed to improve renal function (57). Therefore, the efficacy of perioperative fluid therapy in jaundiced patients remains to be further studied. At any rate, it is crucial to monitor the perioperative blood volume closely and maintain water-electrolyte balance for the sake of protecting renal function.

Effects on the Gastrointestinal System

Obstructive jaundice can damage the gastrointestinal mucosal barrier, causing stress ulcer and intestinal bacterial translocation, which potentially lead to severe adverse clinical outcome, even life-threatening events.

Malnutrition

Malnutrition is common in patients with obstructive jaundice because of their poor gastrointestinal absorption and malabsorption of fats and sterols. The impaired enterohepatic circulation can easily cause fat-soluble vitamin deficiency. Patients with obstructive jaundice are susceptible to night blindness because of vitamin A deficiency. Vitamin D deficiency and chronic cholestasis can lead to hepatic osteopathy. Neuromuscular weakness in children is due to vitamin E deficiency (58), and vitamin K deficiency can decrease vitamin K-dependent clotting factors, thus prolonging the prothrombin time (PT) (59).

Obstructive Jaundice and Stress Ulcer

Postoperative alimentary tract hemorrhage in patients with obstructive jaundice remains a major problem in clinical practice. The incidence of peptic ulcer in jaundiced patients is significantly higher than that in non-jaundiced patients (60), primarily due to decreased appetite caused by hyperbilirubinemia, inefficient digestion and absorption dysfunction because of bile salt deficiency, and malabsorption of lipids and fat-soluble vitamin K in particular.

The Impact on the Gut

Intestinal Mucosal Barrier Dysfunction. Large numbers of clinical and experimental studies have shown that intestinal mucosal barrier damage and increased permeability are important factors caus-

ing sepsis and multi-organ failure in obstructive jaundice (61).

The role of the intestinal mucosal barrier is to prevent intestinal pathogenic substances from entering other tissues, organs and blood circulation through the intestinal mucosa. As the structural basis of the intestinal mucosal barrier, intestinal mucosa epithelial cells and the tight junction between them play important roles in maintaining the intestinal barrier function. When obstructive jaundice occurs, the intestinal barrier function is damaged and gut permeability is increased, enabling intestinal pathogens and endotoxin to invade into the mesenteric lymph nodes, portal vein circulation and the liver. Meanwhile, the accumulation of intrahepatic bile acids significantly inhibits the clearance of Kupffer cells (KC) from the resident macrophages, causing endotoxin spilling into the systemic circulation from the portal vein and sustained release of proinflammatory cytokines, eventually forming gut-derived sepsis and multi-organ failure. The exact mechanism of increased intestinal permeability in obstructive jaundice remains unclear. Imbalance between proliferation and apoptosis of intestinal mucosal cells, a series of changes in tight junction proteins between the intestinal epithelial cells and oxidative stress response in the intestine are closely related to the increased intestinal permeability.

Bacterial Translocation. Bacterial translocation refers to the passage of living bacteria and their metabolites through the intestinal mucosal barrier to extra-intestinal mesenteric lymph nodes and distant organs and tissues. Studies in patients with obstructive jaundice have found that the intestinal mucosal barrier (62) and liver function are damaged, and the incidence of bacterial translocation and endotoxemia is increased markedly (63) in direct hyperbilirubinemia, and at the same time a large number of liver-derived tumor necrosis factors were generated (64). Endotoxemia and TNF are important causes of high morbidity and mortality in model animals and clinical patients (65). Intestinal bacterial translocation and accompanied endotoxin can lead to the release of cellular mediators, activation of humoral and cellular systems, altered activation of the complement system, initiation of the endogenous coagulation pathway and eventually organ dysfunction (66). It is reported that the applica-

tion of glutamine (67), arginine, lactulose (68), yeast (69) and other drugs can ameliorate intestinal mucosal barrier damage, thereby preventing bacterial translocation from occurring.

Change in Immune Function

Immune function, especially cellular immunity, is inhibited in obstructive jaundice (66, 70), while the suppression of immune function is the key factor contributing to the high rate of morbidity and mortality, and poor prognosis in obstructive jaundiced patients (71). Patients with a weakened immune system are more susceptible to endotoxemia than those immunocompetent patients, and endotoxemia in turn can aggravate impairment to the immune function, forming a vicious cycle to cause more severe results. It is also proved that the higher risk of postoperative infection in jaundiced patients is usually associated with the impaired immune function (72). So, rapid and efficient immune recovery is very important for patients with obstructive jaundice.

Preoperative Assessment and Preparation

Preoperative hematocrit < 30%, indirect bilirubin > 200 μ mol/L and malignancy are three independent risk factors determining the prognosis of patients with obstructive jaundice. Hepatocellular dysfunction leads to insufficient protein synthesis, gluconeogenesis and ketogenesis. It is advisable to maintain serum total protein higher than 60 g/L, and albumin at a 30 g/L or higher level. Generally, preoperative coagulopathy can be corrected with intramuscular vitamin K (1-10 mg). It is usually initiated 3 days before surgery. Fresh frozen plasma can be considered when vitamin K is invalid. Several therapeutic strategies could be used to reduce preoperative endotoxemia in patients with obstructive jaundice, including rational use of antibiotics; active liquid therapy; use of lactose with an anti-endotoxin effect; and early enteral nutrition to protect the function of intestinal flora.

Several strategies have also been suggested for pre-operative protection of renal function, including prevention of hypovolemia; avoidance of using nephrotoxic drugs such as aminoglycoside antibiotics and non-steroidal antipyretic analgesics; daily monitoring of liquid intake and

output, renal function and electrolytes; and early treatment with 5%-10% mannitol and avoidance of using low-dose dopamine.

It is usually difficult to improve the poor nutritional status of patients with obstructive jaundice before the relief of the obstruction (73). It is advisable to use high protein, high carbohydrate and low fat diet through the enteral route to increase glycogen reserve. If enteral nutrition is not applicable due to gastric dilatation, nasojejunal tube feeding can be considered. Parenteral nutrition can be initiated 5-7 days before operation and continued after surgery in patients with severe malnutrition (recent body weight loss > 10% - 15% or actual weight < 90% of ideal weight) in whom enteral nutrition is not applicable.

Anesthetic Management

Selection of Anesthesia

Thoracic epidural anesthesia (TEA) is reported to have a protective effect on intestinal barrier function (74). Some studies reported that TEA significantly inhibited the increase of endotoxemia-induced intestinal epithelial permeability, thereby reducing the endotoxin-induced intestinal barrier dysfunction (75), and some others argued that TEA could improve intestinal microcirculation during systemic inflammatory response and increase gastrointestinal local blood flow (76). TEA can provide relatively stable hemodynamics, and does not affect the tissue perfusion of the vital organs, thus playing a role in protecting the intestinal barrier function. Although epigastric surgery can be carried out under epidural anesthesia, potential low blood volume and a wide range of sympathetic blocks could induce severe hypotension. In particular, abdominal exploration or traction of the gallbladder is likely to induce arrhythmia or cardiac arrest due to vagal reflex.

Compared with epidural anesthesia, general anesthesia with endotracheal intubation is safer and has a better anesthetic effect, a lower incidence of hypotension and a good response to ephedrine. However, tracheal intubation has poor drug tolerance and is associated with a relatively high incidence of delayed recovery after general anesthesia.

General anesthesia combined with epidural block can avoid the disadvantages of the above two

methods of anesthesia. It can maintain more stable hemodynamics and provide a perfect anesthetic effect. Meanwhile, it can reduce the consumption of general anesthetics so that patients can wake up quickly and carry out early extubation. In addition, the indwelling epidural catheter can still be used for postoperative analgesia. In short, combined general-epidural anesthesia is a viable option for patients with obstructive jaundice.

Use of Narcotic Drugs and Muscle Relaxants

Muscle Relaxants

The muscle relaxant, which is metabolized through the liver, excreted via the biliary tract, and could slow the heart rate, should not be used in jaundiced patients. Succinylcholine can excite the vagus nerve and is likely to cause bradycardia or ventricular arrhythmia. It is preferable to use short-acting depolarizing muscle relaxants. Neostigmine is cholinergic and therefore should be used with caution to prevent serious arrhythmia or cardiac arrest.

Atracurium and cisatracurium are the choice of muscle relaxants for jaundiced patients, for their metabolism does not depend on the liver and kidney functions. About 8% of these drugs are degraded via Hofmann elimination *in vivo*; a very small amount of them is broken down through acetate metabolism, and the remaining 15% is excreted via the kidney in a prototype form. Repeated use of atracurium or cisatracurium would not cause accumulation of the drug in the body. There is no significant difference in the effect of these two muscle relaxants between genders and age groups (77, 78). The intensity of cisatracurium is 4 times that of atracurium. But its metabolite laudanosine is only one-third of that of atracurium at an equivalent clinical dose and there is no dose-dependent effect of histamine release and no cardiovascular adverse effect.

Rocuronium bromide is widely used for clinical anesthesia due to its short onset time and intermediate duration of action (79). It is eliminated unchanged primarily in bile, while urinary elimination is a secondary pathway (80). Our previous study found that neuromuscular blockade of rocuronium was prolonged in patients with obstructive jaundice, and therefore concluded that impedance of rocuronium excretion may be the primary reason, probably due to bile duct

obstruction and increased plasma unbound rocuronium because of the competition of free bilirubin for albumin binding (81). To reduce the occurrence of pulmonary complications and postoperative residual neuromuscular blockade in the perioperative period, objective neuromuscular monitoring and the use of sugammadex (82) or anti-cholinesterase (83) is recommended.

Inhalation Anesthetics

Obstructive jaundice is often accompanied with liver damage, so hepatonephrotoxic drugs such as halothane should be avoided. Enflurane has no significant adverse effect on liver function and therefore is not contraindicated for use in hepatobiliary patients. Sevoflurane did not seem to cause damage to renal function in patients with cirrhosis who underwent hepatectomy (84).

Our study found that the MAC_{awake} of desflurane was reduced in patients with obstructive jaundice, probably due to hyperbilirubinemia (85). It seems that the higher the plasma bilirubin level is, the lower the MAC_{awake} would be. We also found that the recovery time of patients with obstructive jaundice under sevoflurane anesthesia was prolonged obviously. In addition, the sensitivity to isoflurane was enhanced in jaundiced patients and therefore they were more likely to develop hypotension and bradycardia during anesthesia induction and maintenance as compared with non-jaundiced controls (86). This is likely to induce damage to liver function and alter the neurotransmitter 5-hydroxytryptamine in the CNS due to endotoxemia and hyperbilirubinemia caused by biliary obstruction (87). This may be a target for inhalation anesthetics, with the neurotoxicity of jaundice on the brain, resulting in increased susceptibility to inhaled drugs in obstructive jaundiced patients. Therefore, the dosage of inhalation anesthetics should be relatively reduced in patients with obstructive jaundice, and intraoperative monitoring should be emphasized, especially in patients who receive a single inhalation anesthetic agent.

Intravenous Anesthetics

The choice of intravenous sedatives is very important for general anesthesia induction and intraoperative maintenance in patients with obstructive jaundice. At present, anesthesia of tar-

Table 2. Anesthetic and Postoperative Management of Obstructive Jaundice.

Anesthetic Management of Obstructive Jaundice	
Selection of anesthesia	
Combined general-epidural anesthesia is a viable option	
Use of narcotic drugs and muscle relaxants	
Muscle relaxants	
Succinylcholine: cause bradycardia or ventricular arrhythmia	
Rocuronium bromide: its neuromuscular blockade was prolonged	
Atracurium and cisatracurium: the choice of muscle relaxants	
Inhalation anesthetics	
Halothane: hepatonephrotoxic drugs, should be avoided	
Enflurane :no significant adverse effect ,is not contraindicated for use	
Sevoflurane: the recovery time was prolonged obviously.	
Desflurane: the MACawake was reduced	
Isoflurane: the sensitivity was enhanced	
Intravenous anesthetics	
Propofol: Both the pharmacokinetics and pharmacodynamics were similar and it is safe at low and intermediate doses	
Etomidate:the requirement to reach a level of anesthesia was reduced	
Opioid analgesics	
Analgesics:the dosage can be reduced by about 50%	
Morphine: the dose after operation could be reduced by about 50%	
Fluid management	
Stroke volume variation (SVV): can predict fluid responsiveness	
Pulse pressure variation (PPV): can predict fluid responsiveness	
Static hemodynamic indexes (MAP, CVP, CI): inferior to SVV and PPV	
Postoperative Management of Obstructive Jaundice	
Capacity management : Adequate capacity is needed, the use of furosemide and mannitol could be considered	
Analgesia: adequate, avoid NSAID drugs, use a small dose of opioid analgesics	

get-controlled infusion (TCI) with propofol is still a popular choice. Apfel et al. found that the incidence of postoperative nausea and vomiting with propofol anesthesia was decreased by nearly 20% as compared with that of inhalation anesthesia (88). Our previous research found that several pharmacokinetic parameters and half-time of the three phases ($T(1/2)$ (alpha), $T(1/2)$ (beta), $T(1/2)$ (gamma)) were similar between patients with obstructive jaundiced and non-jaundiced patients and concluded that the pharmacokinetics of propofol was similar in the two groups (89). We also demonstrated that the pro-

propofol pharmacodynamics observed by BIS and MAP remained unchanged under obstructive jaundice with STB from 7.8 to 362.7 micromol/L (90). It is reported that a moderate degree of liver dysfunction does not affect the propofol clearance (91) because of the existence of its extra-hepatic metabolic pathway (92, 93). Low and intermediate concentrations of propofol did not seem to damage cardiac function in bile duct ligation rats (94). In another study, we found that the requirement for etomidate to reach a level of anesthesia was reduced in obstructive jaundiced patients (95).

There are controversies over whether propofol is suitable for patients with obstructive jaundice because of its effect of cardiovascular depression. There is no significant difference in cardiac parameters caused by low and intermediate doses of propofol between rats with cholestasis and sham control rats. But propofol could exaggerate cardiac depression in bile duct ligation rats at high dose (94). Our research found that propofol itself might be able to eliminate the risk factors and protect the cardiovascular function (90). It is also reported that high-dose intravenous propofol during cardiopulmonary bypass reduced postoperative myocardial cell injury as compared with isoflurane or small-dose propofol anesthesia (96). So propofol is safe for jaundiced patients at low and intermediate doses.

Opioid Analgesics

Compared with healthy people, the dosage of analgesics can be reduced by about 50% in patients with obstructive jaundice, probably because of the increased endogenous enkephalin release induced by cholestasis. Our previous study also found that the pain threshold for electrical stimulation was increased significantly in jaundiced patients as compared with that in non-jaundiced patients (1.7 ± 0.3 mA vs. 1.1 ± 0.1 mA), while the dose of morphine after operation could be reduced by about 50% (97). All opioid analgesics can cause biliary sphincter spasm and an increase in bile duct pressure, and this effect of morphine can last for about two hours.

Fluid Management

Fluid administration is one of the essential preventative strategies to control the postoperative complications and mortality in patients with obstructive jaundice (59). The basic aim of the fluid management during the period of operation is to increase the left ventricular stroke volume for avoiding cardiopulmonary complications and interstitial edema (98). Many studies have shown that static variables of preload like central venous pressure (CVP), or pulmonary capillary wedge pressure (PCWP), or left ventricular end-diastolic area (LVEDA) are poor predictors of fluid responsiveness (99). It is reported that Stroke volume variation (SVV) obtained by FloTrac/Vigileo system and the pulse pressure variation

(PPV) obtained by IntelliVue MP system have the ability to predict fluid responsiveness in patients with obstructive jaundice during mechanical ventilation, which may perhaps guide volume management of perioperative jaundice patients (100) and the prediction of fluid responsiveness by static hemodynamic indexes (MAP, CVP, CI) were inferior to SVV and PPV, as reported earlier (99).

It is reported that the presence of extracellular fluid (ECW) depletion (5, 47, 56) was related to hemodynamic and renal disturbances in patients with obstructive jaundice. Giving sufficient solution and providing strong hemodynamic support were the effective therapy to expand the ECW in the perioperative period. And the administration of dopamine associated with appropriate fluid infusion in the peridrainage period has an impact on renal function in selected patients with malignant biliary obstruction, especially in patients with higher marked cholestasis.

Postoperative Management

Adequate capacity is needed for patients with obstructive jaundice after surgery to maintain urine output and, if necessary, the use of furosemide and mannitol could also be considered. Besides, the adequate analgesic effect should be provided after the surgery. And the use of NSAID drugs should be avoided, anesthesiologists and surgeons could use a small dose of opioid analgesics.

Summary

An overview of what we have discussed above shows that a series of pathophysiological changes develop in patients with obstructive jaundice. The physiopathologic changes induced by obstructive jaundice are schematically presented in Figure 1 (61). These changes can pose challenges to anesthesiologists. They should know how to choose suitable anesthesia methods, techniques and drugs, and in the meantime, closely monitor any significant change of vital signs of the patient so as to make early diagnosis and treatment should any unexpected event occur. The anesthetic and postoperative management of obstructive jaundice are summarized in table 2. They should also work closely with surgeons with respect to improving the preoperative preparation

and optimize the physiological condition of the patients with obstructive jaundice so that the perioperative morbidity and mortality of these patients can be reduced significantly.

This work was supported by grants (No. 81571048, and No. 81671039) from the National Natural Science Foundation of China.

The authors declare no conflicts of interest.

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