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REVIEW
Peri and postoperative pulmonary complications among cirrhotic individuals

Sirotik hastalardaki peri ve postoperatif pulmoner komplikasyonlar

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Surgical intervention among cirrhotic individuals carries a high risk for peri-and postoperative complications. We review the literature regarding the frequency and consequences ofpulmonary complications in cases of cirrhosis. The experience with hepatopulmonary syndrome and portopulmonary hypertension in liver transplant recipients is also presented.

Key words: Hepatopulmonary, syndrome, portopulmonary hypertension, pulmonary complications, cirrhosis

Sirozlu hastalarda cerrahi girişimlerin perioperatif ve postoperatif riskleri vardır. Sirozlu hastalarda görülebilecek olan pulmoner komplikasyonların teşhis ve tedavisi literatür ışığında gözden geçirilmiştir. Ayrıca, hepatopulmoner sendromlu ve portopulmoner hipertansiyonlu olgulardaki ortotopik karaciğer transplantasyon deneyimi sunulmuştur.

Anahtar kelimeler: Hepatopulmoner sendrom, portopulmoner hipertansiyon, pulmoner komplikasyonlar, siroz

INTRODUCTION

Patients with advanced liver disease who require surgery are at a greater risk for surgical- and anesthesia-related complications as compared to those with a healthy liver (1). The magnitude of this risk depends upon the type of liver disease, its severity, the surgical procedure to be performed and the type of anesthesia to be used (2).

Marked alterations in vascular tone accompany the development of portal hypertension in patients with advanced liver disease (3, 4). These changes contribute substantially to the onset of clinical overt cardiovascular and pulmonary disease in cirrhotic patients. Hemodynamic alterations occur in both acute and chronic liver disease as well as in individuals with extrahepatic portal hypertension. These changes occur in as many as 30% of cirrhotic patients (5). The hyperdynamic circulatory state of cirrhotics is characterized by splanchnic and systemic vasodilatation and a markedly increased cardiac output (CO). As a result, these patients manifest hypotension, tachycardia and frequently have a cardiac flow murmur. When measured, the CO is markedly increased and the systemic vascular resistance (SVR) is reduced similarly. Thus, the hyperdynamic circulatory state of cirrhosis is similar to that seen in individuals with endotoxemia and sepsis. Endotoxin and cytokine mediated nitric oxide (NO) production contributes substantially to the hyperdynamic circulation in cirrhosis (5, 6).

The relative importance of hepatic dysfunction as distinguished from portal hypertension in triggering this hyperdynamic condition is unknown. Although the hyperdynamic circulatory state is generally more pronounced in individuals with advanced liver disease, a similar state is seen in experimental animals and in humans with extrahepatic portal hypertension, without demonstrable liver dysfunction (7, 8). These findings suggest that both hepatic dysfunction and portal hypertension contribute to the changes in the splanchnic and systemic vasculature occurring as a consequence of NO overproduction. The precise pathogenesis of the hyperdynamic circulatory state is likely multi-

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factorial, and mediators other than NO, such as glucagon, prostaglandins and bile acids, may also contribute to observed vasodilatation (9). This vasodilatation is associated with sodium and water retention, leading to an increase in total body water and ultimately a state of vascular overload.

PULMONARY ABNORMALITIES IN CHRONIC LIVER DISEASE

Pulmonary symptoms and abnormalities occur commonly in patients with chronic liver disease. As many as 70% of cirrhotic patients undergoing an evaluation for liver transplantation complain of dyspnea (10). Arterial blood gas and pulmonary function test abnormalities also are common and are found in as many as 45-50% of cirrhotic patients (11). The causes for pulmonary dysfunction in liver disease have been identified as: i) intrinsic pulmonary disorders not specifically related to liver disease and ii) unique problems secondary to the presence of liver disorders or portal hypertension. Intrinsic pulmonary diseases seen in individuals with liver disease include sarcoidosis, cystic fibrosis, chronic obstructive pulmonary disease (COPD), congestive heart failure, asthma and infections, i.e. pneumonia, abscess, empyema and nosocomial infections (12). Pulmonary abnormalities secondary to liver diseases are usually associated with specific liver diseases, i.e. panacinar emphysema of alpha-1 antitrypsin deficiency (A1AT) and fibrosing or lymphocytic alveolitis/pulmonary granulomas of PBC. Fluid retention due to complicated portal hypertension, ascites/anasarca and hepatic hydrothorax are also common and impair pulmonary function (12).

A small subgroup of cirrhotic individuals develops clinically important pulmonary vascular alterations consisting of either microvascular dilation leading to the hepatopulmonary syndrome (HPS) or arteriolar vasoconstriction leading to portopulmonary hypertension (PPH). These two pulmonary vascular syndromes substantially affect the morbidity and mortality of cirrhotic patients and can influence the individual's candidacy for surgery.

PREOPERATIVE SCREENING FOR LIVER DISEASE

All patients undergoing surgery should undergo a careful history and physical examination to exclude findings or risk factors of liver disease. Prior blood transfusions, tattoos, illicit drug use, sexual promiscuity, family history of jaundice or liver disease, history of jaundice or fever following anesthesia, alcohol use and a current list of medications need to be ascertained. A review of symptoms associated with liver disease to include fatigue, pruritis, increased abdominal girth, jaundice, palmar erythema, spider telangiectasia, splenomegaly, gynecomastia and testicular atrophy should be assessed (13). All patients with potential liver disease should be assessed for the presence of jaundice, coagulopathy, ascites, electrolyte abnormalities, renal dysfunction and encephalopathy, which may require specific additional testing procedures and treatment prior to any anticipated surgery (13, 14).

Essential preoperative screening should include an assessment of arterial oxygenation, chest radiography and Doppler echocardiography (15, 16). Pulmonary function testing is usually reserved for patients with advanced symptomatology. The major symptoms and clinical manifestations of underlying pulmonary disease in cirrhotics include: dyspnea/fatigue (especially in HPS), arterial hypoxemia, pleural effusion, hydrothorax, syncope and chest pain (especially in PPH).

Arterial Hypoxemia

Arterial hypoxemia is defined as a PaO_2 of less than 70 mmHg, an alveolar-arterial oxygen ($A\text{-}aO_2$) gradient of more than 20 mmHg or an oxygen saturation of less than 92%. In cirrhotics these values generally worsen in the standing position (16). Hypoxemia is associated with hepatopulmonary syndrome as well as with severe pulmonary hypertension (15). The prevalence of hypoxemia in individuals with cirrhosis ranges from 14% to 22% (17, 18). Patients with encephalopathy and Child's C liver disease are more likely to be hypoxemic.

Chest Radiography

A preoperative chest X-ray provides a baseline from which subsequent comparisons can be made. In addition, asymptomatic abnormalities (i.e. neoplasm or infection) may be detected, requiring preoperative intervention. Significant pulmonary hypertension may be suggested by the finding of an enlarged central pulmonary artery and cardiomegaly. In patients with progressive dyspnea, the presence of a hydrothorax may be demonstrated.

Doppler Echocardiography

Right ventricular systolic pressure, as determined by transthoracic echocardiography, correlates with measured pulmonary artery systolic pressu-

re. This relationship has been demonstrated in 74 liver transplant candidates with mild to moderate portopulmonary hypertension (pulmonary artery systolic pressure less than 50 mmHg by Doppler echocardiography) (20). Contrast-enhanced echocardiography is also considered a valuable screening test for determining intracardiac shunts as well as the pulmonary vascular dilatations of HPS. This test is not considered clinically necessary unless overt hypoxemia (PaO_2 <70 mmHg) is present (15, 16). In HPS, there is late (four to six cardiac cycles) opacification of the left heart chamber.

Lung Perfusion Scan

Lung perfusion scans are considered to be abnormal if the extrapulmonary uptake is greater than 5% following an injection of technetium-labeled macroaggregated albumin particles. They are used to detect and quantify the degree of intrapulmonary shunting seen in individuals with the HPS (21, 22). Pulmonary angiography is invasive and is not used as a screening test for HPS (23).

Pulmonary Function Tests

Routine pulmonary function testing of all cirrhotics being considered for surgery is probably not necessary (15, 24). Patients with progressive dyspnea, however, should be studied with an assessment of FEV_{1s} FVC and DLCO (16). Symptomatic smokers and patients with AlAT should also undergo preoperative pulmonary function tests.

PULMONARY CONSEQUENCES OF ADVANCED LIVER DISEASE

Hepatic Hydrothorax

Pleural effusions occur in approximately 5% of cirrhotic patients as a direct consequence of portal hypertension (25). These effusions are predominantly right-sided (70%), but may present as bilateral (15%) or be left-sided (15%). The effusions result from the migration of ascites fluid through small diaphragmatic defects. The chemistry of the pleural fluid in cases of hepatic hydrothorax is that of a transudate and is similar to the characteristics of the ascitic fluid from which it originates. Negative pleural pressure occurring with inspiration enables these effusions to occur even in the absence of clinical ascites (25).

Dyspnea in cirrhotics is usually a result of lung compression. Severe hypoxemia (PaO_2 <50 mmHg) is not characteristic of hepatic hydrothorax, and when it occurs other causes of hypoxemia should be explored. Symptoms related to hepatic hydrothorax can be relieved temporarily by thoracentesis. Attempted pleural space obliteration with sclerosing agents frequently fails. The placement of transjugular intrahepatic portosystemic shunts (TIPS) can dramatically reduce the degree of hepatic hydrothorax and the requirement for repeated thoracenteses (15, 26). Unless there is a contraindication, TIPS should be considered as a bridge to orthotopic liver transplantation in these cases.

Hepatopulmonary Syndrome (HPS)

HPS is an uncommon problem, occurring as a result of intrapulmonary microvascular dilatation in a cirrhotic individual. Positive contrast-enhanced echocardiograms are reported to occur in 13 to 47% of cirrhotics, but arterial hypoxemia occurring as a result of HPS is present in only 5-13% (17). In the absence of orthotopic liver transplantation, it is associated with a 40% mortality within 2.5 years following diagnosis. Subclinical intrapulmonary vascular dilatation without hypoxemia usually progresses with worsening oxygenation once initiated (17, 20). Increased levels of exhaled NO are reported to distinguish patients with HPS from those with cirrhosis and normal arterial oxygenation (27).

The pulmonary arterial dilation occurring in chronic liver disease is classified as either being microscopic and diffuse (type I) or macroscopic and discrete (type II). Type I lesions are the most common. Type I pulmonary arterial dilation is associated with severe hypoxemia and responds variably to 100% inspired oxygen (15). Pulmonary angiography is normal in such cases and the pathophysiology is reversible with time after orthotopic liver transplantation. Type II lesions can be demonstrated with computed tomographic (CT) chest scanning or pulmonary angiography, and are associated with severe hypoxemia and a poor response to 100% inspired oxygen (15, 16). These lesions do not respond to liver transplantation and either localized resections or coil embolotherapy is used in these cases (17). The experience with HPS at our institution is summarized in (Table 1).

Portopulmonary Hypertension (PPH)

PPH is defined as the association between pulmonary artery hypertension and portal hypertension (22). Symptoms usually begin as non-specific complaints of fatigue, dyspnea and peripheral edema. Portopulmonary hypertension occurs in 2-4%

Table I. OLTx at NZTI for hepatopulmonary syndrome

#	Gender	Age	Diagnosis	PaO_2 (mmHg)	Treatment	OLTx	Outcome
1	M	40	Cryptogenic	70 (on O_2)	O_2	10/2001	Alive
2	M	55	HCV	68	O_2	12/1995	Expired in 2000
3	F	61	ETOH	58	O_2	Not OLTx candidate	Lost to follow up
4	F	25	Budd-Chiari	56	O_2	3/1995	Expired in 5/1995

NZTI: Nazih Zuhdi Transplantation Institute, OLTx: Orthotopic liver transplantation, HPS: Hepatopulmonary syndrome, PaO_2: Pulmonary artery oxygen pressure

of patients with advanced liver disease, defined by the hemodynamic criteria obtained by right heart catheterization (28). There is a marked hyperdynamic circulatory state, characterized by CO that is greater than that seen in primary pulmonary hypertension (29).

Moderate and severe PPH is a major clinical problem. Such patients are defined by a mean pulmonary artery pressure (MPAP) greater than 35 mmHg, a pulmonary capillary wedge pressure (PCWP) below 15 mmHg and a pulmonary vascular resistance (PVR) greater than 250 dyne/sec/cm^{-5}, as determined at the time of right heart catheterization (30, 31). Cardiac reserve is a major determinant of the clinical course in individuals with PPH. Those without a high CO have poor outcomes (31).

Moderate to severe PPH (untreated or refractory to treatment) remains a relative contraindication to orthotopic liver transplantation. Recent treatment advances with intravenous Epoprostenol may allow successful orthotopic liver transplantation with favorable long term outcomes (32-34). Epoprostenol, a potent pulmonary and systemic vasodilator, has been reported to dramatically improve pulmonary hemodynamics. It has important side effects, which include thrombocytopenia and splenomegaly (32, 34). The experience with PPH at our institution is summarized in (Table 2). Of note is the use of Bosentan (endothelin receptor antagonist) at 125 mg twice a day oral dose, in case #4.

POSTOPERATIVE PULMONARY COMPLICATIONS

It has been estimated that 10% of all patients with liver disease undergo an operative procedure during the final two years of their lives. Many investigators have documented a higher risk of morbidity and mortality associated with abdominal procedures in this group of patients. Common postoperative complications are pneumonia, respiratory failure, bronchospasm, unexplained fever, excessive bronchial secretion, abnormal breath sounds, productive cough, atelectasis, hypoxemia, pneumothorax, cor pulmonale and fluid overload condition (35).

Table 2. OLTx at NZTI for portopulmonary hypertension

#	Gender	Age	Diagnosis	MPAP (mmHg)	Treatment	OLTx	Outcome
1	F	54	PBC	43	Epoprostenol	5/1999	Alive
2	F	49	Autoimmune	45	Nicardipine	11/2000	Alive
3	F	65	Auto/PBC	31	None	1/2002	Alive
4	M	48	HCV	68	Epoprostenol& Bosentan	Listed on the list	Expired while
5	F	60	PBC	33	(-) response to Epoprostenol (-) response to NO	Not OLTx candidate	Lost to follow-up
6	F	60	Autoimmune/ Scleroderma	37	None	Not OLTx candidate	Expired
7	F	50	ETOH	41	Refused	Not OLTx candidate	Lost to follow-up
8	M	59	ETOH	42	Epoprostenol	4/1998	Expired 1 mo. after OLTx

MPAP: Mean pulmonary artery pressure, NZTI: Nazih Zuhdi Transplantation Institute, OLTx: Orthotopic liver transplantation, PPH: Portopulmonary hypertension, NO: Nitric oxide

Postoperative Pneumonia

Despite the advances made in surgical critical care, ventilator-associated pneumonia is associated with a 20-25% mortality rate (36). There are numerous risk factors for ventilator-associated pneumonia, including underlying disease, prolonged mechanical ventilation, direct lung injury and shock. The standard clinical criteria for pneumonia are usually sufficient for diagnosis and risk identification for mortality.

The recognized risk factors for pneumonia include advanced age, preexisting COPD, high Child-Turcotte-Pugh score, male gender, smoking, diabetes mellitus, cryptogenic cirrhosis, elevated serum creatinine, emergency surgery, hypothyroidism, preoperative infection, cardiothoracic surgery and the presence of immunosuppression (36). The incidence of pneumonia is 90% to 100% in cirrhotic patients who had been intubated for more than one week (37).

Pulmonary Embolism

The risk for venous thromboembolism (VTE) is highest among patients who are hospitalized with a history of recent surgery, with a nearly 22-fold increased risk. VTE is particularly common among patients with malignancy and trauma. Serious liver disease is associated with a 90% decrease in risk for VTE. Patients with advanced liver disease often have prolonged clotting times and thrombocytopenia. These impairments of normal hemostasis may act to protect patients with advanced liver disease from VTE (38).

In summary, peri- and postoperative pulmonary complications are common in individuals with advanced liver diseases. In addition, they have unique pulmonary disease (HPS and PPH) processes that adversely affect their clinical status, may limit their acceptance for liver transplantation and which can adversely affect the individual's postoperative course.

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