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REVIEW ARTICLE

Patient preparation before surgery for cholangiocarcinoma

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Abstract

Aim. Multiorgan dysfunction is often encountered in jaundiced patients and may compromise the postoperative outcome after liver resection for cholangiocarcinoma (CCA). The aim of the present study was to elucidate evidence-based medicine regarding the benefit of the available preoperative treatments currently used for the preparation of patients before surgery for hilar CCA. *Material and methods.* An electronic search using the Medline database was performed to identify relevant articles relating to renal dysfunction, bacterial translocation, hemostasis impairment, malnutrition, liver failure, and postoperative outcome in jaundiced patients undergoing liver resection for CCA. *Results.* There is grade B evidence to expand the extracellular water volume and to administer oral synbiotic supplements. Intravenous vitamin K administration is an effective treatment. Perioperative nutritional support should be administered preferably by the enteral route in severely malnourished patients with compromised liver function undergoing extended liver resection (grade A evidence). There is only grade C evidence to recommend a portal vein embolization in patients with CCA when the future remnant liver volume is $<40\%$. *Conclusions.* A simplified scheme that might be useful in the management of patients presenting with obstructive jaundice was presented. Despite surgical technique improvements, preparation of patients for surgery will continue to be one of the major determinants for the postoperative prognosis of jaundiced patients.

Key Words: *Bacterial translocation, hemostasis impairment, Klatskin tumor, liver failure, malnutrition, obstructive jaundice, renal dysfunction*

Introduction

The current standard treatment of hilar cholangiocarcinoma (CCA) is major hepatectomy combined with extrahepatic procedures that include lymphadenectomy, extrahepatic bile duct resection, and, sometimes, portal vein resection [1]. Belghiti et al., in evaluating the operative risk in 747 patients undergoing liver resection [2], observed that the mortality rate was significantly higher in patients with jaundice (21%) compared to that in cirrhotic patients (8.7%) or in patients with normal liver (1%; $p<0.001$). They also demonstrated that a combined extrahepatic procedure was the only independent predictor of in-hospital death in patients with malignancy. Several related abnormalities resulting from obstructive jaundice represent a kind of multiorgan failure and include bacterial translocation [3–6], hemostasis impairment [7], renal insufficiency [8], and increased risk of liver failure [1,9]. Patient preparation before surgery for CCA should therefore be focused on prevention of: 1) bacteremia, 2) malnutrition, 3) hemostasis impairment, 4) renal insufficiency, and, finally, 5) liver failure. The role of preoperative biliary drainage will be discussed in another lecture.

Prevention of bacteremia

The etiopathogeny of bacterial translocation in patients with obstructive jaundice is multifactorial. It includes increased intestinal permeability [5], impaired clearance of endotoxins by Kupfer's cell [4], and altered systemic immunity [3,6]. The risk of postoperative bacteremia has been evaluated in a large series of 407 patients who underwent liver resection [10], the authors showing that the risk of bacteremia was significantly higher in patients with CCA (19%) compared to the risk in those with hepatocellular carcinoma (4%) or liver metastases (3%; $p<0.0001$).

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The multivariate analysis showed that the presence of an obstructive jaundice increased the risk of bacteremia by 4.6% and the performance of an extended hepatectomy by 2.5%, indicating that the bacteremic risk is increased 13 times in patients with obstructive jaundice and undergoing an extended hepatectomy for hilar cholagiocarcinoma [10]. Furthermore, the postoperative complications were significantly associated with the occurrence of bacteremia, particularly liver failure, renal dysfunction, and mortality [10]. The benefit of perioperative synbiotic (lactobacillus and bifidobacterium) treatment was recently analyzed in a prospective randomized trial [11]. In patients receiving synbiotic therapy during the perioperative period, the authors registered a significant reduction in the postoperative infectious complications rate, shorter hospital stay, and reduced length of antibiotic therapy compared to that in patients receiving synbiotic therapy only in the postoperative period [11]. They also demonstrated that perioperative synbiotic treatment enhanced the immune responses, attenuated the systemic postoperative inflammatory reaction, improved the intestinal microbial environment, and reduced the postoperative infectious complications rate [11].

Prevention of malnutrition

During the past decade, most of the relevant progress achieved in the field of liver resection concerns a better understanding of hepatic function and of the metabolic needs of the liver during the perioperative period. The aims of perioperative nutritional support are to reduce the catabolic response, to improve protein synthesis, to accelerate liver regeneration, to decrease the damage of the residual liver, and to reduce postoperative morbidity [12]. No reported series has analyzed the effect of perioperative nutritional support in patients with hilar CCA. Indeed, in 1994 the first randomized study evaluated the effect of perioperative branched-chain amino-acids (valine, leucine, isoleucine) therapy in cirrhotic patients with hepatocellular carcinoma [13]. In patients receiving branched-chain amino-acids nutritional support, the authors observed a reduced rate of overall postoperative morbidity (34% vs 55%) particularly septic complications (17% vs 37%) and an improved postoperative liver function as reflected by less deterioration of the indocyanin green test (ICG-R15) [13]. The same conclusions were reported in another recent series using a similarly enriched diet [14]. Concerning immunonutrition (arginine, omega-3 fatty acids), a prospective randomized study has shown that perioperative enteral immunonutrition is associated with a lower rate of overall postoperative complications in patients undergoing surgery for malignant diseases (9% vs 21% in the control group; $p = 0.02$) [15].

Prevention of hemostasis impairment

Vitamin K deficiency due to intestinal malabsorption and impaired production of coagulation factors are often encountered in patients with obstructive jaundice [7].

Prevention of renal insufficiency

The etiology of renal insufficiency in patients with obstructive jaundice is multifactorial, including extracellular water depletion, myocardial dysfunction, increased plasma levels of atrial natriuretic peptide (ANP), and water and sodium retaining hormones (aldosterone, renin, vasopressin, endothelin ET-1, prostaglandin PGE_2) [16]. A multivariate analysis has shown that the predictors of renal insufficiency in patients with obstructive jaundice are age, serum bilirubin level, renin activity, endothelin (ET-1), prostaglandin ($PG\ E_2$), and urinary sodium excretion, indicating that renal insufficiency is influenced by the intensity of biliary obstruction, by the degree of extracellular water depletion, and by the balance of vasoactive and sodium-water regulating hormones. However, the type (malignant or benign) and location of the bile duct tumor (perihilar or extrahepatic) does not influence the occurrence of renal insufficiency [16]. In a prospective randomized clinical trial, the benefit of extracellular water volume expansion was evaluated in patients with obstructive jaundice undergoing endoscopic drainage [17]. The authors noticed a significant improvement of the creatinine clearance after intravenous fluid administration before any procedure [17]. However, extracellular water expansion failed to improve renal function after endoscopic drainage. These observations are further evidence that the etiopathogeny of renal insufficiency in patients presenting with jaundice is multifactorial.

Prevention of liver failure

Two main factors affecting the occurrence of postoperative liver failure after liver resection are the future remnant liver volume and the quality of the liver parenchyma. While several studies have shown that portal vein embolization is effective in inducing hypertrophy of the non-embolized liver [18–21], the benefit of portal vein embolization has not been definitively validated in a randomized controlled trial. Indeed, a prospective non-randomized study has shown no benefit of portal vein embolization before right hepatectomy in patients with normal underlying liver parenchyma [22]. However, another series has shown that portal vein embolization before an extended hepatectomy is justified when the estimated future remnant liver volume is $<25\%$ [23]. In our experience of portal vein embolization performed in 146 patients when the future remnant liver volume was less than 30% of the total functional liver volume,

the time required to obtain an adequate liver hypertrophy was shorter in patients with normal liver [24]. Abdalla et al. noticed that the future remnant liver volume correlated with postoperative outcome [21]. They showed significantly higher complication rates in patients with a future remnant liver volume of <20% [21].

Only two retrospective studies focused on portal vein embolization and biliary cancers [25,26]. The largest series reported 240 consecutive patients undergoing portal vein embolization before an extended hepatectomy for biliary cancer with a mortality rate of 9% [26]. Underlining an improvement in the mortality rate over the study periods, i.e. changing from 17.9% between 1991 and 1995 to 4.8% after 2001, the authors performed portal vein embolization when the future remnant liver volume was <40%. The second retrospective series showed neither mortality nor liver failure with 40% 5-year survival in 58 patients who underwent extended hepatectomy for hilar CCA [25]. These good results might be explained by a higher cut-off in the decision to perform portal vein embolization. Indeed, if, in jaundiced patients, the liver volume to be resected was more than 50%, the authors performed portal vein embolization before surgery. Then, after adequate liver regeneration, liver resection was achieved only when the total bilirubin level was more than twice the upper normal limit. In the absence of jaundice, the decision to perform hepatectomy was based on the liver function test estimated by the ICG-R15. In patients with normal ICG-R15 ($\leq$10%), portal vein embolization was performed when the future remnant liver volume was <40%. However, for patients with abnormal ICG-R15 test (>10%), portal vein embolization was performed when the future remnant liver volume was <50% of the total functional liver volume. In accordance with all the above reported series, where should the volumetric cut-off be for performing portal vein embolization in patients with jaundice due to hilar CCA? No evidence-based answer can be drawn from the literature, but the following several factors should be considered when deciding on portal vein embolization: 1) the ratio of future remnant liver/total liver volume, 2) the presence of any underlying liver parenchyma injury (particularly cholestasis), 3) the presence of comorbidities (diabetes mellitus and/or malnutrition which inhibit liver regeneration), and 4) the necessity of a combined extrahepatic procedure.

Consensus statements

- There is a benefit of preoperative oral administration of synbiotic treatment in jaundiced patients scheduled to undergo extended hepatectomy combined with extrahepatic procedures.
- Perioperative nutritional support is indicated for patients with severe malnutrition, with preoperative compromised liver function, and undergoing extended liver resection. Branched-chain aminoacids immunonutrition should be administered preferably by the enteral route beginning one week before surgery.
- Intravenous vitamin K administration is an effective treatment.
- There is a need to expand the extracellular water volume in the preoperative period.
- Portal vein embolization is a key procedure in the preoperative management of patients with hilar CCA; it allows indications for liver resection to be extended safely and the resection margins in a curative intent increased. Portal vein embolization is recommended in patients with CCA when the future remnant liver volume is <40%. Liver resection should not be performed earlier than 3 weeks after portal vein embolization.

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