Management of Postoperative Hepatic Failure

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Hepatic resections are increasingly performed in the United States and across the world for both primary malignancies and metastatic disease.[1,2] A number of factors have contributed to this trend, including improved imaging and diagnostics; evolution of surgical instruments; and improved technique, including enhanced intraoperative and postoperative management. More effective chemotherapy for metastatic colorectal cancer, the rising incidence of hepatitis and hepatocellular carcinoma (HCC), and the expansion of hepatectomy for non-colorectal metastatic disease are other important factors.[3-7] With the growing frequency of liver resection, outcomes after hepatectomy have improved steadily during the last 20 years. In high-volume centers, mortality after hepatectomy is now routinely reported to be <5% for metastatic disease and <10% for primary HCC.[8-13]

The most feared complication after hepatectomy is development of progressive and refractory postoperative hepatic failure (POHF), which has been reported to occur in 1.2% to 32% of cases in the literature.[14] Irrespective of whether this presents as fulminant failure with rapidly progressive jaundice, coagulopathy, encephalopathy, and multi-organ failure in the first few days after surgery, or as a slow but inexorable rise in bilirubin over weeks, the end result can be bleak. Mortality occurs in an estimated 1.6% to 2.8% of cases.[15,16] Despite improvements in perioperative management, POHF remains a challenge, even at highly specialized high-volume academic centers.[16] A number of factors contribute (Table 1) and, although careful patient selection by surgeons who carry out high-volume liver operations has played an important role in improving outcomes, hepatectomy is being performed increasingly in older and higher-risk patients.[6,8,17] In addition, technical advancements have allowed experienced surgeons to push the boundaries, particularly among patients with colorectal cancer liver metastases, with increasingly aggressive resections that include extended resections (trisectionectomy); major vascular resections and reconstructions; 2-stage resections, including associated liver partition and portal vein ligation for staged hepatectomy; and even ex vivo resections.[18-20] Concurrently, however, the increasing use of chemotherapeutic agents, such as oxaliplatin and irinotecan, can cause hepatocellular toxicity, such as chemotherapy-associated steatohepatitis. This injury can compromise hepatic regenerative capacity and lead to POHF.[21-23] Finally, there has been a dramatic increase in the incidence of viral hepatitis in North America, principally due to the hepatitis C virus, and, therefore, HCC.[4,24] The majority of these patients have hepatocellular injury with varying degrees of fibrosis or cirrhosis. Orthotopic liver transplantation (OLT) can offer the best treatment for these patients, but is only applicable in a minority of such patients due to limitations in organ availability and the strict tumor and patient criteria that permit transplantation.[25,26] As such, POHF continues to be a feared complication, as more extensive hepatic resections are undertaken.

DEFINITION OF POSTOPERATIVE HEPATIC FAILURE

Historically, a wide variety of definitions for POHF or hepatic insufficiency have been described in the literature.[27-31] A standardized and reproducible definition, however,

Table 1. Risk Factors for Development of Postoperative Hepatic Failure

Risk factors
Older age (older than 70 y)
Male sex
Cirrhosis
Fibrosis
Hepatitis (viral or other)
Intraoperative blood loss
Requirement for blood transfusion
Prolonged operative time
Ischemia
Obstructive cholestasis
Preoperative chemotherapy
Steatosis/steatohepatitis
Extended hepatectomy
Small future liver remnant
Preoperative hypoalbuminemia

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Abbreviations and Acronyms

ALI = acute lung injury
FFP = fresh frozen plasma
FLR = future liver remnant
HCC = hepatocellular carcinoma
INR = international normalized ratio
ISGLS = International Study Group of Liver Surgery
OLT = orthotopic liver transplantation
POHF = postoperative hepatic failure
PVE = portal venous embolization
SFSS = small for size syndrome
TBW = total body water
TIPS = transjugular intrahepatic portosystemic shunt

remains somewhat elusive. A simple and intuitive definition offered by Jarnagin and colleagues[32] is "prolonged hyperbilirubinemia unrelated to biliary obstruction or leak, clinically apparent ascites, prolonged coagulopathy requiring fresh frozen plasma (FFP), and/or hepatic encephalopathy."

In recent reports, much emphasis has been placed on establishing firm criteria that define POHF. These criteria are intended to aid surgeons during the selection process in predicting which patients with increased risk of progressive deterioration in the postoperative period, as well as to help define POHF in a uniform manner that will allow comparison of outcomes among multiple institutions. Balzan and colleagues[33] proposed the "50-50 criteria," which includes a prothrombin time <50% (equates to an international normalized ratio [INR] approximately >1.7) and serum bilirubin >50 μmol/L (3 mg/dL) on postoperative day 5, as accurate predictors of liver failure and death. When analyzing a heterogeneous group of 775 patients undergoing elective resection, including fibrotic and cirrhotic patients, the authors found that those who met the 50-50 criteria had a 59% mortality (up to 60 days from index admission) vs just 1.2% in those who failed to meet these somewhat arbitrarily chosen parameters. Mullen and colleagues[16] used receiver operating characteristic curve analysis to define POHF in a group of 1,059 noncirrhotic patients and found that a peak bilirubin >120 μmol/L (7 mg/dL) was strongly predictive of morbidity and 90-day mortality. Both groups proposed that their respective definitions of POHF be adopted as standard.

Most recently, the International Study Group of Liver Surgery (ISGLS) provided a consensus definition and severity grading of posthepatectomy liver failure.[14] This definition was: "postoperative deterioration in the ability of the liver to maintain synthetic, excretory, and detoxification functions, characterized by an increased INR and elevated bilirubin on, or after, postoperative day 5." The 3 grades of severity include liver failure resulting in abnormal laboratory parameters but without change in clinical management of the patient (grade A), failure resulting in deviation from regular clinical management of patients but not requiring invasive therapies (grade B), and, finally, failure resulting in deviation from the regular postoperative course and requiring invasive management (grade C). The authors agreed that in all patients and grades of severity the alternative causes of hyperbilirubinemia, such as biliary obstruction, must first be ruled out.

Authors from the University of Heidelberg applied the criteria to 835 patients who underwent liver resection between 2002 and 2008, and noted that 65 patients (11%) met the ISGLS criteria for POHF; 8% were grade A, 72% were grade B, and 20% were grade C failures, with mortality rates of 0%, 12%, and 54%, respectively, thereby validating the definition and grading system in that patient cohort.[34]

Although the ISGLS consensus definition appears to have come closest to a standardized definition of POHF, it is clear that there is not a precise point of no return. In the reports by Balzan[33] and Mullen[16] and their colleagues, 41% and 67% of patients, respectively, who met the designated threshold criteria for POHF recovered, despite a challenging postoperative course. Therefore, exact definitions alone matter less than anticipation, avoidance, and implementation of management strategies to recover such patients.

PATHOPHYSIOLOGY OF POSTOPERATIVE HEPATIC FAILURE

The pathophysiology of POHF is likely very similar to that of small for size syndrome (SFSS), which is occasionally observed after split and living-related OLT.[35] Inadequate functional liver mass after hepatectomy is implicated in both POHF and SFSS. However, size alone does not seem to reliably predict POHF.[36] After major hepatectomy, residual liver size increases rapidly during the first 2 weeks through a combination of regeneration and hypertrophy, both of which are compromised in cirrhotic livers.[29,37] After both extended hepatectomy and partial-liver transplantation, excessive portal flow through the small remnant appears to result in activation of multiple inflammatory cascades, with the subsequent recruitment of inflammatory cells and release of inflammatory cytokines that ultimately contribute to sinusoidal injury.[38,39] In transplantation patients, data assessing venous hemodynamics suggest that excessive portal perfusion can result in graft injury, as shown by a direct significant correlation between bilirubin levels and recipient portal venous flow in

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