Original Research Article

Cirrhosis aggravates the ninety-day mortality after liver resection for hepatocellular carcinoma

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ABSTRACT

Background: Ninety-day postoperative mortality (90-D POM) measures accurately the liver resection-related mortality. In cirrhotic patients, reporting post-hepatectomy-related death only as in-hospital or thirty-day postoperative mortality (30-D POM) may underestimate cirrhosis-related death after liver resection.

Methods: Medical records of adult cirrhotic (cirrhosis group) and matched non-cirrhotic (control group) patients, who underwent elective liver resection at Sohag University Hospital (April 2014- March 2018), were analyzed. The 90-D POM versus in-hospital mortality and 30-D POM were compared in both groups.

Results: Forty-six patients (23 per group) were eligible for the study. Liver resection was carried out in all cirrhosis group patients for hepatocellular carcinoma (HCC). In the control group, liver resection was indicated for colorectal metastasis (13), benign masses (7) and intrahepatic cholangiocarcinoma (3). Compared with the control group, cirrhotic patients exhibited significantly higher complication rates (p<0.05), prolonged hospital stays (p<0.05), increased postoperative levels of serum bilirubin and reduced prothrombin concentration (p<0.05). In the control group, in-hospital mortality and 30-D POM were zero while 90-D POM was 4%. In the cirrhosis group, the in-hospital mortality and 30-D POM were identical (8.7%), however the 90-D POM was significantly higher and almost doubled (17%).

Conclusion: Liver cirrhosis triggers significant mortality that may extend for ninety days postoperatively. In cirrhotic patients, post-hepatectomy death should be reported as 90-D POM rather than the obviously misleading in-hospital mortality or 30-D POM.

Key words: Cirrhosis, Hepatocellular carcinoma, Liver resection, 90-day postoperative mortality

INTRODUCTION

Evaluation of in-hospital mortality or 30-D POM, as measure of postoperative death induced by liver resection, has been shown to be inadequate and profoundly misleading. Both parameters were limited by clear underestimation of the impact of surgical intervention on the rates of postoperative death. In contrast, several studies showed that 90-D POM precisely reflects the extent of postoperative mortality following major hepatobiliary and gastrointestinal tract surgical procedures. For instance, the sensitivity of 90-D POM to capture surgery-related post-operative death was remarkably higher in comparison with 30-D POM after gastrectomy and colectomy procedures. Moreover, the mortality rates reported within the first month after esophageal and pancreatic resections were doubled within two months later. Similar doubling of 30-D POM was reported after lung resections and cytoreductive surgery for ovarian cancer within ninety days postoperatively. The normal liver parenchyma exhibits unique capacity of regenerating its lost volume after partial resection. The distinctive capability of the liver to reestablish its volume allowed remarkable progress in liver resection surgery. Nevertheless, liver regeneration is influenced not only by the size but also by the quality of the remnant liver...
parenchyma. Therefore, liver cirrhosis, steatosis, steatohepatitis, cholestasis and advanced age are well known for reducing the tolerance of the liver to ischemia insults during hepatectomy and remarkably hindering liver regeneration. Among hepatic parenchymal diseases cirrhosis has been given much attention. Liver cirrhosis denotes common consequence of infection with chronic hepatitis C virus (HCV) and chronic hepatitis B virus (HBV). Cirrhosis of the liver is linked to the development of hepatocellular carcinoma (HCC) in most HCC patients.

In Egypt, HCC is a very prevalent source of cancer incidence and mortality among men. The high incidence of HCC in Egypt is clearly attributed to high prevalence of chronic viral infection of the liver especially HCV. Due to the functional derangements and defective capacity of regeneration in the setting of cirrhosis, patients with liver cirrhotic are more vulnerable to postoperative complications, including mortality, after partial liver resection.

Despite the reduced sensitivity of 30-D POM to adequately detect surgery-related death, it remains widely used to assess post-hepatectomy mortality in patients with cirrhosis-related HCC in Egypt. Therefore, we designed this study to compare 90-D POM versus in-hospital death and 30-D POM after liver resection in cirrhotic patients compared with matched control group of non-cirrhotic patients.

METHODS

Medical records of patients who underwent elective liver resection at Sohag University Hospital (April 2014 to March 2018) were analyzed. Two groups of adult patients with age 18 years or more who underwent elective liver resection in the setting of liver cirrhosis (cirrhosis group) versus non-cirrhotic patients (control group) who were operated for a variety of liver masses were included. Both groups are matched for age, American Society of Anesthesiologists’ (ASA) score, technique of liver transection and number of resected segments. Exclusion criteria from the study were age less than 18 years, liver trauma, emergency resections (such as ruptured HCC), combined liver and other organ resections, preoperative chemotherapy and radiation therapy, pre- and/or postoperative radiofrequency tumor ablation and/or transarterial chemo-embolization within the first three months after liver resection and preoperative platelet count less than 100,000/μL.

Preoperative evaluation

Standard clinical evaluation comprised detailed medical history and clinical examination, including abdominal ultrasonography. Routine laboratory tests entailed serologic tests for HBV and HCV, complete blood count, measurement of plasma levels of bilirubin, albumin, aspartate transaminase (AST) and alanine transaminase (ALT), creatinine and random glucose level. Basic study of the coagulation profile was carried out by determination of prothrombin time and concentration. The levels of relevant tumor marker, including alpha-fetoprotein (α-FP) in all cirrhotic patients and carbohydrate antigen 19:9 (CA 19:9) and/or carcinoembryonic antigen (CEA) in selected patients were measured. Cirrhotic patients were assigned Child-Pugh class according to bilirubin, albumin and prothrombin measurements, clinical evaluation for hepatic encephalopathy and abdominal ultrasonography for assessment of ascites. Diagnosis of portal hypertension was based on endoscopic documentation of esophageal varices and/or a combination of splenomegaly with reduced platelet count of less than 100,000/μL. Preoperative imaging entailed standard triphasic computerized tomography (CT) scans of the abdomen to identify and characterize liver mass lesions and to precisely detect their number, location and their relation to major intrahepatic vessels. Typically, liver mass was labelled as HCC in patients with viral hepatitis-related cirrhosis when it shows enhancement during the arterial phase followed by portal venous wash out. Vascular invasion was presumed when tumor thrombus with similar enhancement pattern was located in the portal or hepatic veins. Contrast enhanced CT of the chest was ordered in patients with high levels of α-FP (>200) and suspicion of hepatic vascular invasion such as presence of HCC in close anatomical relation to the major hepatic veins, their tributaries, the portal vein or its segmental branches. Partial hepatectomy was carried out in patients with technically resectable tumor(s) when an adequate volume of future liver remnant (FLR) is expected based on preoperative volumetric studies. The option of liver resection was offered to patients within the Milan criteria of liver transplantation if they refuse or cannot afford liver transplantation. Resected liver tumor(s) were evaluated histopathologically for the number, dimensions and grade of differentiation, vascular invasion, and status of margin of the resected specimen(s). Vascular invasion was histopathologically defined as invasion of main portal vein or one of its branches or invasions of a main hepatic vein or its tributaries. Complete resection (R0) was concluded when at least one centimeter of tumor-free resection margin(s) was confirmed microscopically. An experienced hepatologist who was blindly made all histopathologic assessments of resected specimens.

Anesthesia and surgical approach:

Operative procedures were undertaken consistently in all patients by the same team of surgeons and anesthesiologists. The abdominal cavity was accessed via bilateral subcostal incision. The peritoneal cavity and abdominal viscera were routinely examined for malignant ascites and metastatic deposits. In cirrhotics, extensive mobilization of the liver and unnecessary dissection of hepatic ligaments were avoided to decrease bleeding and to minimize the potential for postoperative ascites and provocation of portal hypertension. Parenchyma...
transsection was carried out under intermittent hepatic inflow occlusion by application of a vessel loop as tourniquet around the hepatoduodenal ligament. Low central venous pressure (0-5 mm H₂O) with adequate urine output were maintained during liver transection. Parenchyma transection was performed by incising the Glisson’s capsule using electrocautery and crushing of the liver parenchyma by small artery forceps. Large intrahepatic vessels and bile ducts (≥3 mm) were ligated or clipped, smaller vessels were cauterized. Transected hepatic veins were usually secured by running sutures.

**Evaluation of postoperative complications**

Postoperative complications included several events such as intra-abdominal hemorrhage, bile leak, ascites, intraperitoneal abscess, postoperative liver failure (manifested by jaundice, bleeding tendency and encephalopathy) and wound infection. Three definitions of liver resection-related mortality as postoperative death (a) within the same hospital admission, (b) during the first postoperative 30 days or (c) during the first postoperative 90 days even after discharge from the hospital were recorded and compared. The severity of postoperative complications was ranked according to Clavien-Dindo classification. For each patient, an overall score of postoperative complications (ranging from one to seven) was calculated by assigning one point to each of grades I, II, IIIa, IIIb, IVa, IVb and V in ascending order as previously reported. Statistical analysis was carried out by GraphPad Prism 6.0 software.

**RESULTS**

According to the study protocol, forty-six patients were eligible for enrollment (23 per group). Twenty-eight patients were males. The ASA score was I for all patients. All cirrhotic patients had Child-Pugh class A. All patients in cirrhosis group had HCC and chronic HCV infection. Liver resection was indicated in the control group due to colorectal liver metastasis in thirteen patients, benign lesions in seven patients (including 3 giant hemangiomas, 2 focal nodular hyperplasia, 2 inflammatory pseudotumor and one hemangioendothelioma) and intrahepatic cholangiocarcinoma in three patients (Figure 1). A summary of demographic and pre-operative clinical data is shown in Table 1. Liver transection was performed using the clamp crushing technique in 38 patients and a vessel sealing device in the remaining eight. Twenty-six patients (thirteen per group) underwent major liver resection (3 segments). Operative data are summarized in Table 2.

**Impact of cirrhosis on postoperative complications**

Postoperative complications score was significantly higher in the cirrhosis compared with the control group (Table 3). A subgroup analysis in the cirrhosis group comparing patients who developed postoperative thrombocytopenia <100,000/µL (four patients) versus those who did not (nineteen patients) showed significant increase in postoperative complications in cirrhotic patients who had coexistence postoperative thrombocytopenia (p<0.05).

**Table 1: Demographic, clinical and preoperative laboratory data.**

<table>
<thead>
<tr>
<th>Laboratory data</th>
<th>Cirrhosis</th>
<th>Control</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bilirubin (mg/dl)</td>
<td>1 (0.7-1)</td>
<td>0.7 (0.6-1)</td>
<td>ns</td>
</tr>
<tr>
<td>Albumin (g/dl)</td>
<td>3.8 (3.5-5)</td>
<td>4.7 (3.8-5.1)</td>
<td>&lt;0.05*</td>
</tr>
<tr>
<td>Prothrombin concentration (%)</td>
<td>80 (70-106)</td>
<td>88 (80-110)</td>
<td>ns</td>
</tr>
<tr>
<td>Hemoglobin (g/dl)</td>
<td>12 (11-15)</td>
<td>13 (11-15)</td>
<td>ns</td>
</tr>
<tr>
<td>Creatinine (mg/dl)</td>
<td>0.8 (0.8-1)</td>
<td>0.9 (0.7-1)</td>
<td>ns</td>
</tr>
</tbody>
</table>

**Table 2: Operative data in cirrhosis versus control group.**

<table>
<thead>
<tr>
<th>Duration of surgery (minute)§</th>
<th>Cirrhosis</th>
<th>Control</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Central venous pressure cm/H₂O</td>
<td>2 (1-3)</td>
<td>2 (1-4)</td>
<td>ns</td>
</tr>
<tr>
<td>Blood loss (ml)§</td>
<td>780 (350-1250)</td>
<td>450 (300-750)</td>
<td>&lt;0.05*</td>
</tr>
<tr>
<td>Red blood cell transfusion (unit)§</td>
<td>2 (0-3)</td>
<td>1 (0-2)</td>
<td>&lt;0.05*</td>
</tr>
<tr>
<td>Plasma transfusion (units)§</td>
<td>3 (0-6)</td>
<td>0 (0-1)</td>
<td>&lt;0.05*</td>
</tr>
</tbody>
</table>

Significant difference, § Median (range).
Cirrhosis impairs postoperative synthetic functions of the liver

Plasma levels of albumin and prothrombin concentration in the fifth postoperative day (POD-5) were considered as markers of recovery of the synthetic functions of the remnant liver.

The median values of both were significantly reduced in the cirrhosis compared with the control group (Table 3). Within the cirrhosis group, the values of both markers were significantly lower in the 4 patients who developed postoperative thrombocytopenia <100,000/µL compared with the remaining 19 patients who higher postoperative platelet count.

Table 3: Postoperative data in cirrhosis versus control group.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Cirrhosis</th>
<th>Control</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Albumin (g/dl)</td>
<td>2.9 (2.5-5.0)</td>
<td>3.8 (3.5-4.8)</td>
<td>&lt;0.05*</td>
</tr>
<tr>
<td>PC (%)</td>
<td>67 (56-104)</td>
<td>90 (77-106)</td>
<td>&lt;0.05*</td>
</tr>
<tr>
<td>Bilirubin (mg/dl)</td>
<td>1.6 (0.8-5)</td>
<td>0.8 (0.5-1.2)</td>
<td>&lt;0.05*</td>
</tr>
<tr>
<td>Highest complication score</td>
<td>7 (2-7)</td>
<td>2 (1-3)</td>
<td>&lt;0.05*</td>
</tr>
<tr>
<td>Length of hospital stay</td>
<td>14 (9-42)</td>
<td>9 (4-18)</td>
<td>&lt;0.05*</td>
</tr>
<tr>
<td>Length of ICU stay</td>
<td>6 (1-14)</td>
<td>1 (0-2)</td>
<td>&lt;0.05*</td>
</tr>
</tbody>
</table>

Significant difference. *Median (range) PC, prothrombin concentration; POD, postoperative day; ICU, intensive care unit

Liver resection-related mortality in cirrhotic versus non-cirrhotic patients

In the control group, one patient died (4% mortality) during hospitalization on the 25th postoperative day (similar rate of in-hospital mortality and 30-D POM) due to septic complications. In the cirrhosis group, two patients died (8.7% mortality) during the initial 30 days postoperatively while still in-hospital (equal rate of in-hospital mortality and 30-day POM) due to post-hepatectomy liver failure. Noteworthy, both patients had postoperative thrombocytopenia <100,000/µL. The 90-day POM rate was doubled as additional two patients (total mortality increased to 17.4%) died during the initial three months postoperative. Both patients failed to recover normal liver functions postoperatively and suffered from progressive hepatocellular failure.

DISCUSSION

This study demonstrates that the 90-day POM after liver resection in cirrhotic patients was almost doubled compared with both in-hospital mortality and 30-day POM. These findings highlight the remarkable underestimation of the negative impact of cirrhosis on post-hepatectomy mortality rates when reported as in-hospital mortality or 30-day POM. Moreover, the increased mortality in cirrhotic patients was associated with decreased postoperative platelet count, with likely impairment of liver regeneration.

The 90-day POM was reported as an accurate measure of surgical intervention-induced death almost 3 decades ago; when Gonwa and co-workers reported on mortality incurred by liver transplantation in patients with hepatorenal syndrome.26 Likewise, in a large cohort of 2597 liver resection patients, the traditional 30-d POM was 5.7%, a figure that was misleading and significantly obscuring the actual post-hepatectomy mortality rates which reached 8.3% and 10.1% within 60 and 90 days, respectively.27

In the setting of gastrointestinal cancers, the reporting 30-day POM was not sufficient to precisely identify surgery-related mortality in cirrhotic patients.

Figure 1: (B) Left hepatectomy for giant hemangioma (control group).
induced postoperative death following array of major surgical procedures, including esophagectomy, gastrectomy, colectomy, proctectomy, partial hepatectomy and pancreatcetomy. Alternatively, the 90-day POM was more sensitive to recognize postoperative deaths that were directly related to surgery. Several studies have reported similar results following surgery for pancreas cancer, gall bladder cancer, esophageal cancer, emergency colonic surgery, liver tumors, liver transplantation and even for lung cancer and cytoreductive surgery for ovarian cancer.\textsuperscript{2,6,10,11,28-31}

However, most of the clinical studies which documented the superiority of the 90-D POM as a measure of liver resection-related mortality enrolled only a minority of cirrhotic patients.\textsuperscript{2,6,28,30}

Our results showed increased overall complication score among cirrhotic patients compared with the non-cirrhotic controls. This finding accords with Hacklet al, who reported an up to 50% increase of postoperative morbidity, including postoperative liver failure, bleeding, impaired healing and sepsis, after liver resections in cirrhotic compared non-cirrhotic patients.\textsuperscript{32} Likewise, we found that cirrhotic patients required significantly prolonged stays in the hospital and in the intensive care units. These events were logically attributed to the reduced power of the cirrhotic liver to recover its lost volume during surgery.\textsuperscript{2,3} In addition, the lower quality of liver parenchyma combined with suboptimal functions exacerbate the susceptibility of the cirrhotic liver to surgical trauma with subsequent increase in postoperative complications, including mortality.\textsuperscript{2,3,32}

As markers of impaired hepatocellular function, cirrhotic patients showed significantly increased levels of serum bilirubin and reduced coagulation capacity. These events are in line with previous reports on increased mortality after liver resection with persistent derangement of bilirubin metabolism and coagulation pathway after liver resection.\textsuperscript{2,3,34}

Interestingly, reduced postoperative platelet count was observed exclusively in the cirrhosis group. This finding, together with the essential role of platelets and platelet derived serotonin, could adequately explain the reduced capacity of restoration of liver functions as well as increased mortality among cirrhotic patients.\textsuperscript{35-37}

The advantages of the case-matched control study design include its excitability and low-cost in relatively short time. Additionally, it enables accomplishment of a study in low number of patients. Therefore, it circumvents the inadequacy that could be imposed by enrollment of small groups of patients due to the strict inclusion criteria. Nevertheless, the inherent limitation of the case-matched control methodology such as the difficult matching of each case with appropriate control and the inability to eliminate the selection bias and potential confounding factors should clearly mentioned.\textsuperscript{38}

CONCLUSION

In conclusion, post-hepatectomy associated mortality should be reported as 90-D POM rather than the misleading in-hospital mortality or 30-D POM, particularly in patients with liver cirrhosis. Increased liver resection-related mortality is associated with reduced postoperative platelet counts with likely impairment of liver regeneration.

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