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ORIGINAL ARTICLE

Correlation of the ICG test with risk factors and postoperative outcomes following hepatic resection

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Summary

Purpose: *Liver failure is a major cause of early mortality following hepatectomy. The future-remnant liver function is an important factor when assessing the risk for postoperative liver functional impairment. Several techniques have been established for this evaluation, including the indocyanine green (ICG) test. The aim of this study was to evaluate the ICG clearance in patients scheduled for liver resection regarding perioperative and postoperative risk factors.*

Methods: *Thirty-one patients, scheduled for liver resection, underwent the ICG test. Peri-operative and postoperative variables were recorded and analyzed using non-parametric tests.*

Results: *Procedures extended from wedge excisions to extended hepatectomies. Plasma disappearance rate (PDR) was found positively correlated with total blood loss, transfusion and operation duration. There were 11 primary hepatic malignancies, including hepatocellular carcinomas and cholangiocarcinomas, 13 metastatic carcinomas, mainly of colorectal origin, and 7 benign lesions. The uninvolved liver parenchyma was normal in 20 (64. 5%) cases. Two patients died due to myocardial infarction and postoperative liver failure, respectively.*

Conclusion: *The role of residual liver function and particularly the hepatic reserve assessment on liver surgery may be of most benefit in the routine stratification of risk, enabling surgical procedures to be performed with safety. The ICG clearance markers were found significantly correlated with perioperative risk factors in histologically 'normal' liver parenchyma. In addition to computed tomographic (CT) volumetry, functional assessment of the hepatic reserve with the ICG test may persuade the preoperative planning and prevent postoperative liver failure.*

Key words: *complications, hepatic reserve, ICG test, liver resection, postoperative liver failure*

Introduction

Evaluation of liver function is a critically important tool for selecting patients for liver surgery. While modern technology has rendered liver surgery a safe procedure, the possibility of postoperative liver failure remains an important concern, especially in cases where a major hepatectomy is planned [1]. Thus, prediction of postoperative residual functional liver parenchymal mass and reserve during preoperative assessment are of paramount importance in order to minimize the surgical risk, especially in patients with hepatocellular carcinoma where the majority of patients may also have liver cirrhosis.

The approaches used to assess liver function and evaluate hepatic reserve either measure the products of liver synthesis or monitor the hepatic clearance function. These tests have been developed to assess the metabolic status of the liver by monitoring the hepatic clearance and allow for calculations concerning the maximum liver volume that can be resected.

The most widely used of these tests is the ICG test. ICG is a synthetic dye that is eliminated by the liver without extrahepatic metabolism or excretion and its blood clearance has been applied to determine the operative risk before hepatectomy.

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Interpretation of this method is based on PDR and retention rate extrapolated to 15 min (R_{15}), both measured by the principle of pulse densitometry, which is an easy and accurate approach [2]. Clearance is considered to be impaired when 10% or more of the dye remains in the plasma 15 min following the injection of 0.5 mg/kg of ICG. Therefore, the compromised biliary ICG excretion correlates with decreased hepatic adenosine triphosphate (ATP) concentration and this decrease in hepatic energy status may reflect a poor hepatic reserve. Nevertheless, controversy still exists about the value of this test, as variations in total hepatic blood flow may affect the retention rate of ICG, and consequently alter the preoperative assessment for hepatectomy [3].

In this study we examined the correlation of the preoperative ICG values with perioperative variables as well as with the outcome of patients who underwent hepatectomy. Our preliminary results were previously reported and are updated herein [4]. Hence, the aim of the present study was to evaluate the ICG test with respect to risk factors for morbidity and mortality in patients undergoing liver resection.

Methods

The study was approved by the Hospital Review Board. All patients gave written informed consent. This prospective, open-label clinical study was conducted between January 2010 and June 2011 in Aretaieion University Hospital, Athens, Greece. Patients scheduled for hepatectomy during this time period were included in the study. All hepatectomies were performed by the same surgical team.

Preoperatively we recorded patients' age, gender, height, weight, body surface area (BSA), albumin and bilirubin levels, international normalized ratio (INR), platelet count, alkaline phosphatase (ALP), serum creatinine and γ-gloutamyl-transferase (γ-GT).

Blood sampling and measurements

All patients underwent the ICG test the day before surgery. The solution was prepared by injecting 5 ml water for injection into the ICG-PULSION vial (PULSION Medical Systems AG, Munich, DE), which contains 25 mg of the dye, thus making a solution of 5 mg/ml. A single bolus uniform injection of 0.5 mg/kg of the dye was administered through a peripheral venous catheter and the PDR (normal values 18-25 %/min) and the R_{15} (normal values 0-10 %), were measured by the LiMON device (PULSION Medical Systems AG, Munich, DE), using the principle of pulse densitometry.

Perioperatively we recorded the volume of transfused packed red blood cells (PRBC), the duration of Pringle's maneuver and the total duration of the procedure. Total liver volume was calculated according to the URATA formula [5] and the volume of the excised parenchyma was measured before formaldehyde submersion. The remaining liver volume was calculated accordingly. The duration of postoperative hospitalization, postoperative complications, as well as the serum bilirubin and INR levels on the 1st, 3rd and 5th postoperative days (POD) were recorded.

Table 1. Demographics and preoperative data of 31 patients included in the study.

Demographics and preoperative data	
Age, years (range)	69 (29-91)
Gender, N (%)	
Male	19 (61.3)
Female	12 (38.7)
Height (cm)	170 (155-187)
Weight (kg)	78 (41-120)
BSA (m^2)	1.91 (1.35-2.48)
Serum albumin (g/L)	3.8 (2.7-4.2)
Serum bilirubin (mg/dL)	0.6 (0.4-20.4)
INR	1.00 (0.90-1.96)
Child-Pugh score, N (%)	
A	28 (90.3)
B	3 (9.7)
C	0 (0)
Platelet count (10^9/L)	257 (143-439)
Alkaline phosphatase (U/L)	91 (44-365)
G-gloutamyl transferase (U/L)	46 (7-534)
Serum creatinine (mg/dL)	0.9 (0.6-1.9)
PDR (% /min)	21.2 (13.1-29.7)
R_{15} (%)	4.7 (1.2-14.0)

Values are presented as medians (range). PDR: plasma dissapearance range, BSA: body surface area, INR: international normalized ratio

The primary aim of the study was the correlation of PDR and R_{15} with preoperative, intraoperative and postoperative variables. The secondary aim was the investigation of factors affecting hospital stay, morbidity and mortality.

Statistics

Statistical analysis was conducted with IBM SPSS v20.0 software (International Business Machines Corp., NY, USA). Spearman's rank correlation test was used to look for bivariate correlations, considering p values of <0.05 as statistically significant.

Results

Thirty-one patients (19 male and 12 female) were included in the study with a median age of 69 years (range 29-91). None of the patients was

Table 2. Intraoperative and pathology data of 31 patients included in the study

Data assessed	
Number of segments resected *	2 (1-5)
Transfusion (mL)	600 (0-3.000)
Pringle duration (min)	25 (0-50)
Operation duration (h)	3.0 (1.0 – 7.0)
Total liver volume (mL)	1,386.56 (955.77-2,896.00)
Specimen liver volume (mL)	700.00 (84.59 – 1,661.97)
Remnant liver volume (mL)	734.81 (188.94-1,398.21)
Maximum lesion diameter (cm)	7.0 (1.0-19.5)
Specimen liver weight (g)	268 (36-2,700)
Status of liver parenchyma (N %)	
Normal	20 (64.5)
Mild fatty infiltration	5 (16.1)
Moderate fatty infiltration	2 (6.5)
Chronic active hepatitis	4 (12.9)

Values are presented as medians (range). *One patient subjected to 2 wedge resections was stratified as subjected to segmentectomy

Child C score and none of the patients had ascites or encephalopathy preoperatively. The preoperative median PDR and R_{15} values were 21.2%/min and 4.7%, respectively.

Patient characteristics are presented in Table 1. The median duration of the surgical procedure was 3 h with a median blood loss of 600 mL. Procedures extended from wedge excisions (stratified as resection of one segment) to resection of 5 segments. Intraoperative data are summarized in Table 2.

As far as histopathology data are concerned, there were 11 primary hepatic malignancies, including hepatocellular carcinomas and cholangiocarcinomas, 13 metastatic carcinomas, mainly of colorectal origin, and 7 benign lesions. The uninvolved liver parenchyma was normal in 20 (64.5%) cases. Mild fatty infiltration was found in 5 (16.1%) cases, moderate fatty infiltration in 2 (6.5%) and active chronic hepatitis was present in 4 (12.9%) cases. Intraoperative and pathology data are summarized in Table 2.

Postoperative complications were stratified as minor (necessitating no interventional procedure), moderate (managed by interventional procedures) and major (deaths and other conditions associated with mortality). Minor postoperative complications included 9 cases of pleural effusion, 2 cases of chest infection, 3 cases of wound infection and 4 cases of minor bile leak without need for interventional treatment. Moderate postoperative complications included 1 case of subhepatic abscess which was treated with percutaneous drainage, 4 cases of bile leak treated with percutaneous drainage of perihepatic bile collections, 1 case of bile leak treated with ERCP, 1 case of subphrenic abscess and 1 case of pleural effusion managed with percutaneous drainage. Major complications included 1 case of a non-ST elevation myocardial infarct, 1 case of inferior vena cava thrombosis, 2 cases of liver insufficiency and 1 case of renal failure. Two patients died on 3rd POD and 10th POD due to myocardial infarction and postoperative liver failure, respectively. Median postoperative hospital stay was 10 days, ranging from 3 to 34 days. The postoperative data are summarized in Table 3.

Table 3. Postoperative serum bilirubin levels, INR levels, and hospital stay of 31 patients included in the study

Bilirubin, INR and postoperative hospital stay assessment	
1st POD serum bilirubin (mg/dL)	1.4 (0.5-28.3)
3rd POD serum bilirubin (mg/dL)	1.2 (0.5-21.7)
5th POD serum bilirubin (mg/dL)	1.1 (0.5-20)
1st POD INR	1.26 (0.99-1.88)
3rd POD INR	1.18 (1.01-1.61)
5th POD INR	1.15 (0.92-1.66)
Postoperative hospital stay (days)	10 (3-34)

Values are presented as medians (range). POD: postoperative day

Statistical analysis

PDR and R_{15} were found to have a statistically significant two-tailed correlation ($p<0.05$). PDR was found positively correlated with total blood loss and transfusion (correlation coefficient: 0.396 and 0.441 respectively; p=0.027 and p=0.013 respectively) and with operation duration (correlation coefficient: 0.389; p=0.031; Figure 1). Neither PDR nor R_{15} demonstrated correlation with major postoperative factors such as postoperative complications or postoperative bilirubin and INR.

Regarding the secondary outcomes, postoperative hospital stay was statistically significantly correlated with higher preoperative values of ALP (correlation coefficient: 0.492; p=0.005), γ-GT (correlation coefficient: 0.367; p=0.042), total blood loss (correlation coefficient: 0.399; p=0.026), Pringle maneuver duration (correlation coefficient: 0.505; p=0.004), procedure duration (correlation coefficient: 0.416; p=0.020), resected liver volume (correlation coefficient: 0.446; p=0.012), complications ($p<0.001$), postoperative bilirubin (p=0.032) and INR (p=0.018). The presence of postoperative

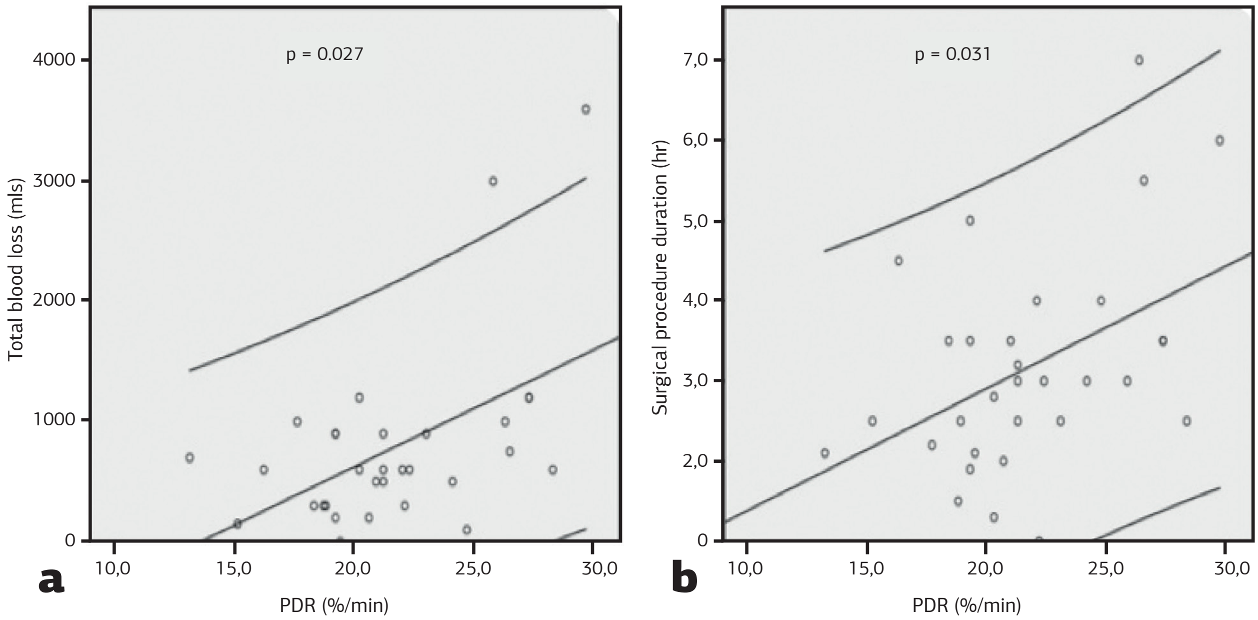

Figure 1. (**a**) Correlation of plasma dissapearance rate (PDR) and total blood loss (p=0.027), and (**b**) PDR and surgical procedure duration (p=0.031).

complications was statistically significantly correlated with the duration of Pringle maneuver (correlation coefficient: 0.468; p=0.008), with the duration of the procedure (correlation coefficient: 0.374; p=0.038), with higher specimen volume (correlation coefficient: 0.417; p=0.020), with 5th POD serum bilirubin (p=0.046), with 1st (p=0.022) and 5th POD INR (p=0.031), and with hospital stay (p=0.041).

Discussion

ICG clearance is a process mediated by hepatocytes, reflecting their ability to uptake and excrete [6]. Consequently, ICG clearance is an effective way to assess the preoperative liver function, and the safety of the planned liver resection in terms of postoperative liver failure likelihood. However, the ICG test has some limitations. Not only patients with normal R_{15} values may suffer postoperative liver failure, but also patients with increased preoperative R_{15} values may proceed to an uncomplicated hepatectomy [7].

In our study, the positive correlation between PDR and operation duration, as well as with total blood loss, is an original finding, and possibly attributed to bulkier underlying disease. Larger tumor volume requires more extensive resections, which again require longer procedures and greater blood loss. Intraoperative blood loss is one of the main risk factors for postoperative liver failure [8]. Fourteen out of 31 patients underwent major hepatectomy (2-5 segments). Nevertheless, although the removal of up to 75% of the total liver volume is possible in patients with normal hepatic parenchyma, perioperative tolerance of resection and the ability to regenerate the missing parenchyma may differ among patients. Complicated recovery and even late deaths may occur, further indicating the importance of hepatic reserve. As there was not a significant correlation between PDR and R_{15} values and specimen liver volume or remnant liver volume in our study, we presume that the intraoperative bleeding could be attributed to poor hepatic reserve. We provide this hypothesis based on pathology data, where the uninvolved liver parenchyma was histologically normal in 20 (64.5%) cases as well as the proper preoperative work up, classifying these patients in a low risk status and good candidates for hepatectomy.

Regarding cirrhotic patients, the clinical assessment of hepatic function has evolved from the Child-Pugh system that was originally developed to predict the risk of mortality in patients undergoing shunting procedures for portal hypertension. However, its role has been expanded to predict risk for a range of procedures including hepatectomy. Most Western Centers would not advocate resection in a Child-Pugh grade C and only very limited resections in patients with Child-Pugh grade B cirrhosis. Hence, liver resection is generally only considered in patients with grade A cirrhosis and it is in this group that quantitative liver function tests may help discriminate among those with apparently normal liver function but whose hepatic reserve may be severely limited. Additionally, the model for end-stage liver disease (MELD) is an alternative clinical scoring system with the advantage of including renal function in predicting outcome and hence may improve prognostic accuracy. Nevertheless, for patients with non-cirrhotic livers, neither MELD nor Child-Pugh can be used to predict risk of postoperative liver failure. For these patients, clinical judgment and functional liver assessment may be the only means of predicting the risk of liver dysfunction postoperatively.

As a small number of patients were studied, complications and relevant deranged postoperative markers, especially liver-failure related, were not frequent enough for a significant correlation to be detected. Yet, the results concerning the secondary outcomes were as expected. More extensive surgical procedures require longer duration of Pringle maneuver, are associated with higher blood loss and are accompanied by more frequent and more severe postoperative complications [9-12]. The aforementioned factors as well as a suboptimal preoperative liver function, associated with higher ALP and γ-GT values, are accompanied by longer postoperative hospitalization. Finally, the detected correlations between complications, hospital stay and postoperative serum bilirubin and INR are consistent with the well-established "50-50 criteria" [13].

Conclusions

While many parameters are used to indicate high risk patients for liver surgery, it is unlikely that a single method dictates safe limits of resectability. Moreover, as far as cirrhotic patients undergoing surgery are concerned, preoperative assessment is required to separate out the "good" Child-A from the "bad" regarding the hepatic reserve for a safe hepatectomy. Therefore, determining technical resectability should focus on preserved structures and liver function rather than those which require resection. These goals may be achieved by a combination of CT volumetry and functional assessment tests of the hepatic reserve, such as the ICG test. Nevertheless, although ICG clearance studies are widely reported in the literature, there are not enough data to delineate the correlation of this test with other parameters that may affect its results, such as body weight and serum creatinine, and to provide definite answers to the importance of the combined functions of the hepatic parenchyma.

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