Using Indocyanine Green Test to Avoid Post-hepatectomy Liver Dysfunction

Chen-Fang Lee, MD; Ming-Chin Yu, MD; Liang-Mou Kuo, MD; Kun-Ming Chan, MD; Yi-Yin Jan, MD; Miin-Fu Chen, MD; Wei-Chen Lee, MD

Background: Post-operative hepatic failure is the most important concern for hepatocellular carcinoma (HCC) patients undergoing hepatectomy. The aim of this study was to determine the safe line of hepatectomy to prevent liver failure.

Method: Clinical profiles of 117 patients with HCC who underwent hepatectomies in Chang Gung Memorial Hospital from Jan. 2002 through Jun. 2003 were reviewed. Patients with heart disease, azotemia, intra-operative blood loss ≥ 1500 ml or international ratio of prothrombin time ≥ 1.2 were excluded. All 117 patients studied had preoperative 15-minute retention rates of ICG (ICG_{15}). Whole liver volumes (LV) were calculated from the equation: LV (ml) = 706.2 x body surface area (BSA, m^2) + 2.4. The resected liver volumes were measured by pathologists. Postoperative liver dysfunction was defined as an international prothrombin ratio of ≥ 1.5.

Results: Thirteen of the 117 HCC patients experienced postoperative liver dysfunction. The relationship between ICG_{15} retention rates and the ratio of remnant liver volume (RR) in the patients with postoperative liver dysfunction was established by regression, producing an equation: RR = 1.98 x ICG + 0.3672 ($r = 0.92$, $p < 0.001$).

Conclusion: Hepatectomies will be safer if the estimated ratio of remnant liver volume prior to surgery is higher than the calculated value of RR = 1.98 x ICG + 0.3672.

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Key words: hepatocellular carcinoma, hepatectomy, indocyanine green test, liver volume

Hepatocellular carcinoma (HCC) is a common malignancy worldwide. The treatment options for HCC include hepatic resection,[1] liver transplantation,[2,3] transcatheter arterial chemoembolization, and local ablation of the tumors. Surgery, including hepatectomy and liver transplantation, offers the best opportunity for the patient to be cured of HCC. The best survival rate for liver transplantation is achieved when the tumor status falls within the Milan criteria.[4] However, hepatic resection remains the major surgical treatment for HCC, especially in Asia, where liver donation is generally lacking.

In cases of hepatic resection, postoperative liver failure is the major cause of early postoperative death.[5,6] Given the risk of hepatic failure, it is important to consider liver function reserve prior to resec-

From the Department of General Surgery, Chang Gung Memorial Hospital, Taipei, Chang Gung University College of Medicine, Taoyuan, Taiwan.
Received: May 2, 2006; Accepted: Jan. 4, 2007
Correspondence to: Dr. Wei-Chen Lee, Department of General Surgery, Chang Gung Memorial Hospital. 5, Fusing St., Gueishan Township, Taoyuan County 333, Taiwan (R.O.C.) Tel: 886-3-3281200 ext. 3366; Fax: 886-3-3285818; E-mail: weichen@cgmh.org.tw

tion. In patients with cirrhosis, fatty liver or concomitant hepatitis, liver function reserve is reduced.[7] To prevent postoperative hepatic failure, the extent of liver parenchyma removal must be based on the individual liver's functional reserve for each patient. In general, hepatic surgeons are aware that excessive nontumorous liver resection or intraoperative hypoxic injury increases the possibility of postoperative liver failure, however, it remains difficult to determine on a case-by-case basis just how much is too much.

Many parameters are employed to represent the functional reserve of the liver.[8-12] The 15-minute retention rate for indocyanine green (ICG_{15}) is the most common preoperative test for evaluating hepatic functional reserve.[13,14] When hepatectomy is carried out on a patient with a high ICG_{15} retention rate, the volume of non-tumorous liver resected must be minimized. However, it is risky to simply rely on the ICG_{15} value to decide how much liver volume may be resected. This retrospective study was performed to address the relationship between ICG_{15} retention rates and the ratio of remnant liver volume in order to determine the safe line for hepatic resection.

METHODS

Patients

One hundred seventeen HCC patients who underwent hepatectomy in Chang Gung Memorial Hospital between January 2002 and June 2003 were enrolled in this study. To focus on the application of the ICG test and to minimize the influence of other variables on hepatic resection outcomes, medical histories were reviewed and patients with heart disease, azotemia, a preoperative international ratio (INR) of prothrombin time (PT) greater than 1.2 or intra-operative blood loss of greater than 1500 ml were excluded. On the first postoperative day, liver function was measured for all patients. Postoperative hepatic dysfunction was defined as an INR of PT greater than 1.5.

Indocyanine green test

All the patients in this study had preoperative ICG_{15} tests. Indocyanine green tests consisted of injecting 0.5 mg/kg of ICG into a peripheral vein, drawing a blood sample from another site 15 minutes later. Results were expressed as the percentage of ICG retained 15 min (ICG_{15}) after the injection.

Liver volume

The standard volume for the whole liver (LV) was calculated with the equation, LV (ml) = 706.2 x body surface area (BSA, m^2)+2.4.[15] Body surface area was calculated using body weight (BW) and body height (BH) (DuBois formula), $BSA = BW(kg)^{0.425} \times BH(cm)^{0.725} \times 0.007184$.[16] Because the density of the liver is approximately 1 g/ml, resected liver volume (RV) was measured by weighing the specimen and subtracting the tumor volume. Tumor volume was calculated with the formula: tumor volume = 0.52 x $width^2$ x length.[17] Thereafter, the ratio of the volume of remnant liver to the whole liver was represented as (RR) = (LV-RV)/LV x 100%. Regression was performed to demonstrate the relationship between ICG_{15} retention rates and the ratio of remnant liver volume to total liver volume.

Statistics

The relationship between remnant liver volume and ICG_{15} values was determined by linear regression and calculated by Sigmastat software. *p* values less than 0.05 were considered statistically significant.

Continuous variables were expressed as mean ± SD and compared using Independent Samples t-Test. Categorical variables were compared using the x^2 test. *p* values less than 0.05 were considered statistically significant. All statistical analyses were performed with SPSS 11.5 for Windows software (SPSS, Inc., Chicago, IL, USA).

RESULTS

Clinical character of the patients

Among the 117 HCC patients enrolled in this study, 97 were males and 20 females, with a mean age of 57 (21~82) years. Fifty-nine (50.4%) had major hepatic resections (namely, removal of 3 segments or more) and 58 had minor hepatic resections. Sixty-nine cases (59%) were patients with chronic hepatitis, including 46 HBV patients, fourteen HCV patients and nine patients with dual hepatitis. Liver cirrhosis was noted in 64 patients (54.7%).

Liver volume and ICG_{15} values

To determine guidelines for evaluating preoper-

ative ICG_{15} values in hepatic parenchymal resection, the characteristics of patients with and without liver failure were compiled and listed in Table 1. Differences between the two groups were significant in terms of remnant liver volumes (RR), remnant liver ratios and operative times. The relationship between the ratio of remnant liver volume and the pre-operative ICG_{15} value for all patients is shown in Fig. 1. Of these patients, thirteen experienced liver dysfunction post-hepatectomy (indicated by blackened circles) and three died of liver failure.

Regression between ratio of remnant liver volume and pre-operative ICG_{15} value

A regression was performed to find the relationship between the ratio of remnant liver volume and the pre-operative ICG_{15} value for the thirteen patients who experienced post-hepatectomy hepatic dysfunction. The results showed a linear relationship between the ratio of remnant liver volume and the pre-operative ICG_{15} (Fig. 1). An equation, $RR = 1.98 \times ICG_{15} + 0.3672$ ($r = 0.92$, $p < 0.001$), could thus be established. By putting pre-operative ICG_{15} values into this equation, the minimal remnant liver volume required to avoid post-hepatectomy liver dysfunction can be calculated. If the estimated ratio of remnant liver volume prior to hepatectomy is lower than the ratio of remnant liver volume calculated by this equation, post-operative liver dysfunction will likely occur.

Table 1. Profiles of Patients with and without Postoperative Liver Dysfunction

	With liver dysfunction (n = 13)	Without liver dysfunction (n = 104)	*p* value
Age (years)	57 ±12.6	57 ±13.0	0.932
Sex (male: female)	12:1	85:19	0.463
No. with hepatitis	5 (38.5%)	64 (61.5%)	0.111
No. with liver Cirrhosis	7 (54%)	57 (55%)	0.948
ICG_{15} (%)	12.86 ±8.6%	11.75 ±8.3%	0.577
Calculated whole liver volume (ml)	1194 ±101	1200 ±130	0.882
Remnant liver volume (ml)	744 ±245	987 ±245	0.001
Remnant liver ratio (%)	62 ±18.4	82 ±17.5	< 0.001
Operative time (min)	329 ±123	238 ±85	0.001
Blood loss (ml)	581 ±363	401 ±343	0.080

Data expressed as mean ± SD.

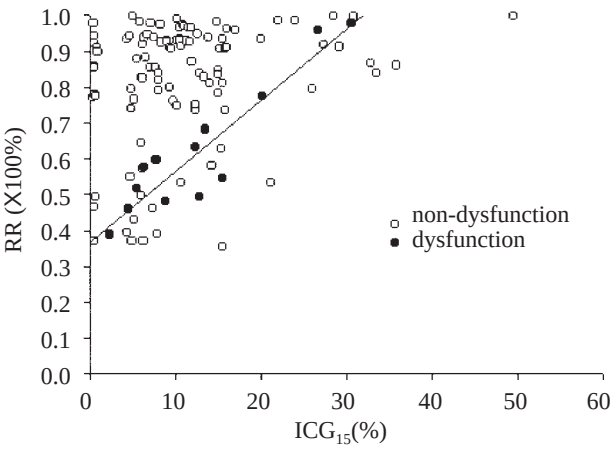

Fig. 1 The relationship between ratio of remnant liver volume and pre-operative ICG_{15} values for 117 patients. An equation was established based on thirteen patients who experienced postoperative liver dysfunction.

DISCUSSION

Using this equation, a safe resection ratio can be predicted, based on individual ICG_{15} retention rates prior to hepatectomy. Hepatectomy will be safer if the ratio of remnant liver volume is higher than the value of $RR = 1.98 \times ICG + 0.3672$. If the resection volume exceeds the ratio of remnant liver volume calculated by this equation, the risk of liver dysfunction will increase.

An ICG_{15} value of 14% has been proposed as a cut-off for identifying patients who will suffer postoperative morbidity following a major hepatic resection.[10,18] However, it is difficult to determine how much liver parenchyma can be resected for an individual patient based solely on an ICG_{15} value of 14%. In our formula, when RR = 1, the ICG_{15} is equal to 32%. Therefore, if the ICG_{15} is greater than 32%, postoperative liver dysfunction is more likely to occur. On the other hand, if the ICG_{15} is 0%, the ratio of remnant liver volume will equal 0.3672. This means that in patients with good liver function, a maximum of about 63% of liver parenchyma can be safely resected. This recommendation concurs with a study by Kubota et al. proposing that a maximum of 60% nontumorous liver can be safely resected.[19] In fact, if we put the regression line onto Fig. 1, we can see that 83% of patients without liver dysfunction fall above the regression line. That is, if we use this

formula to calculate the resection ratio prior to hepatectomy using individual ICG_{15} retention rates, a sensitivity of 83% and specificity of 92% may be expected.

Preoperative safety evaluation in hepatic resection can be performed by combining liver volume with a quantitative liver function test, such as the ICG_{15} used for this study. Remnant liver volume is an essential factor associated with postoperative hepatic failure. Computed tomography volumetry provides a valuable assessment parameter,[19,20] but it is time-consuming and not cost effective. We calculated the resection ratio using body weight and height, rather than CT volumetry.

Because hepatectomy can be performed safely on patients with good liver function reserve and small resection volumes, most patients without hepatic dysfunction (indicated by empty circles) are distributed in the upper left part of Fig. 1. Because patients with heart disease, azotemia, blood loss ≥ 1500 ml or INR ≥ 1.2 were excluded from this study, the formula may not be suitable for patients with major systemic diseases; the resection ratio that can be tolerated by these patients may be smaller than that estimated using the formula.

In conclusion, we have established an equation for avoiding post-hepatectomy liver dysfunction using regression to reveal the relationship between the ratio of remnant liver volume and ICG_{15} values. This study demonstrates that minor or major hepatectomies may be performed safely on select patients if preoperative ICG retention rates are measured. By applying this formula to patients preparing to undergo hepatectomy, we have established references for determining a safe resection ratio of the liver volume (Table 2). Nonetheless, successful outcomes for hepatectomy are dependent not only on the ICG_{15} and the ratio of remnant liver volume, but also on meticulous surgical technique and skilled perioperative care.

Table 2. References for Safe Resection Ratios of Liver Volume

ICG	Safe resection ratio of liver volume
0	< 63.3%
~5	< 53.4%
~10	< 43.5%
~15	< 33.6%
~20	< 23.7%
~25	< 13.78%
~30	< 3.88%
~32	0%

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應用靛氰綠滯留測試避免肝切除術後之肝衰竭

李正方 游明晉 郭亮鋒 詹昆明 詹益銀 陳敏夫 李威震

背 景：肝衰竭是肝切除手術後最重要的問題。切除的肝體積必須根據病人本身之肝功能加以取捨；我們嘗試去分析肝切除後殘餘體積比 (ratio of remnant liver volume; RR) 和 15 分鐘靛氰綠滯留測試 (indocyanine green test; ICG) 之間與肝衰竭的相關性是否存在。

方 法：本研究共收錄在 2002~2003 年之間一百一十七例接受肝切除的肝癌患者。肝切除後殘餘體積比 RR = LV-RV / LV x 100% (LV: liver volume；RV: resected liver volume)。從身高體重換算成體表面積 (body surface area; BSA) 後，肝體積 LV 可由公式 LV (ml) = 706.2 x BSA (m^2) ＋2.4 得來；切除肝體積 RV 則根據病理科檢體報告估計。

結 果：一百一十七位病人中共有十三例發生肝衰竭 (定義爲國際標準凝血時間比 International Normalized Ratio (INR) > 1.5)，將這十三例的病人 RR 和 ICG 作簡單線性迴歸，可得到公式：RR = 1.98 x ICG ＋0.3672 (迴歸係數 r = 0.92, $p < 0.001$)。換言之，根據病人不同之 ICG 可換算出可安全切除的最大範圍。其敏感度及專一度可達 83% 及 92%。

結 論：這個方法可以簡單預測肝臟切除手術的安全界線，但用於患有嚴重內科疾病的病人身上則必須更爲保守。

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關鍵詞：肝癌，肝切除，靛氰綠滯留測試，肝體積

長庚紀念醫院 台北院區 外科部 一般外科；長庚大學 醫學院
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通訊作者：李威震醫師，長庚紀念醫院 外科部 一般外科。桃園縣333龜山鄉復興街5號。Tel.: (03)3281200轉3366; Fax: (03)3285818; E-mail: weichen@cgmh.org.tw