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Assessment of hepatic reserve for indication of hepatic resection: how I do it

Wei-Chen Lee and Miin-Fu Chen

Department of General Surgery, Chang-Gung Memorial Hospital and Chang-Gung Medical School, 5 Fu-Hsing Street, Kwei-Shan Hsiang, Taoyuan, Taiwan

Abstract
Background/purpose. Hepatic resection may result in liver failure in patients with cirrhotic livers. Preoperative evaluation of liver function in cirrhotic patients, to prevent postoperative liver failure, is very important.
Methods. Sixteen patients with hepatocellular carcinoma in cirrhotic livers were enrolled in this study. Liver function was determined quantitatively by monoethylglycinexylidide (MEGX) formation from the metabolism of lidocaine. The whole liver volume and tumor volume were measured by computed tomographic volumetry. The volume of resected liver was recorded by water displacement. The relationship between liver function and remnant liver volume was determined.
Results. A relationship between the percentage remnant liver volume and ratio of MEGX formation after hepatectomy was found. The regression equation was: (postoperative MEGX formation/preoperative MEGX formation) $\times$ 100% = (0.688 $\times$ percentage remnant liver volume + 0.179) $\times$ 100% (r^2 = 0.49). A relationship between MEGX formation after hepatectomy and the international ratio (INR) of prothrombin time was also found. The regression equation was INR = 1.99 − 0.01 $\times$ MEGX (r^2 = 0.30).
Conclusions. Post-hepatectomy liver function can be estimated for an individual patient by the appropriate regression equations. Prevention of post-hepatectomy liver failure for patients with cirrhotic livers is feasible.

Key words Hepatectomy · Liver · Function · Hepatocellular · Carcinoma · Monoethylglycinexylidide

Introduction

Hepatocellular carcinoma (HCC) is one of the most common malignant tumors in Taiwan, and has been the leading cause of cancer death for male patients in recent years. Surgery, including hepatic resection and liver transplantation, is the only hope to cure patients of HCC. However, in Taiwan, liver transplantation is only available for a limited number of patients with HCC because organ donation is lacking. Therefore, hepatic resection has become the most important therapeutic option to cure patients of HCC.

Currently, the overall surgical mortality of hepatectomy has been reduced to less than 5%.[1,2] However, most of the post-hepatectomy hepatic failures and mortality occur in cirrhotic patients. In Taiwan, 60%–70% of the HCC patients have hepatitis B, and another 20%–30% of the HCC patients have antibody to hepatitis C.[3,4] Therefore, 50%–70% of the patients with HCC are associated with liver cirrhosis.[3,4] How to evaluate the liver function exactly in these cirrhotic patients, and how to estimate the hepatic reserve after hepatectomy to prevent liver failure is very important.

Monoethylglycinexylidide (MEGX) is formed from the metabolism of lidocaine by oxidative N-deethylation by the hepatic cytochrome P-450 system. Its formation is a novel quantitative liver function test and has proven to be a highly sensitive and specific indication of liver dysfunction.[5,6] The rate of MEGX formation decreases in patients with chronic liver diseases, and increases when liver function recovers. Liver volume can be measured by computed tomography, and the parenchymal resection rate can be calculated preoperatively. By correlating the findings of remnant liver volume after hepatectomy and MEGX formation, liver function reserve after a hepatectomy can be estimated, to prevent postoperative liver failure for cirrhotic livers.

Patients and methods

Patients

Sixteen patients, 14 men and 2 women, who had hepatic resection for HCC at Chang-Gung Memorial Hospital

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from August to December 2003, were enrolled in this study. The age range of the patients was 34 to 71 years, with a median of 57.5 years. All patients had cirrhotic livers, proved by the pathologic pictures. Thirteen patients (81.3%) were positive for surface antigen of hepatitis B, 2 patients (12.5%) had antibodies to hepatitis C, and 1 patient showed dual positivity for surface antigen of hepatitis B and antibody for hepatitis C.

Quantitative liver function test

The lidocaine metabolite, MEGX, was used as a quantitative liver function test. Lidocaine, 1 mg/kg body weight, was injected intravenously over a 1-min period. Venous blood samples were taken before and 15 min after the lidocaine injection for the measurement of MEGX formation. MEGX formation was measured by fluorescence polarization immunoassay (Abbott Laboratories, North Chicago, IL, USA) as previously described elsewhere.[5] All the patients in this study had the MEGX formation test preoperatively and on the first postoperative day. The percentage of liver function reserve was calculated as: (preoperative MEGX formation/postoperative MEGX formation) $\times$ 100%.

The percentage of liver resection

The whole liver volume and tumor volume were measured by computed tomography volumetry. The volume of resected liver was measured by water displacement. The percentage of parenchymal resection was calculated as: (resected liver volume — tumor volume)/(whole liver volume — tumor volume) $\times$ 100%. The percentage of remnant liver volume was equal to (1-parenchymal resection percentage) $\times$ 100%.

Statistics

The relationship between remnant liver volume and quantitative liver function was determined by linear regression. Hospital stay in two groups with different MEGX levels was compared by the Mann-Whitney rank sum test. An r^2 value of more than 0.25 and P value less than 0.05 were considered statistically significant.

Results

Hepatectomy and liver volume

Based on the design of this study, whole liver volume, tumor volume, and resected liver volume were determined. The median (interquartile range) volume of whole liver in the patients was 1124.5 cm^3 (1044 to 1215 cm^3). The median (interquartile range) volume of the tumor was 47.5 cm^3 (20 to 134 cm^3). The types of hepatic resection included six right hemihepatectomies, four left hemihepatectomies, and six segmentectomies. The median (interquartile range) volume of resected liver was 295 cm^3 (162.5 to 750 cm^3). The median percentage (interquartile range) of liver parenchyma resection was 24% (11.9% to 53.8%). Therefore, the median percentage (interquartile range) of remnant liver parenchyma was 76% (46.3% to 88%). The median (interquartile range) amount of blood loss during operations was 450 ml (250 to 650 ml). Only four (25%) patients had blood transfusion. The amount of blood transfusion was less than 2 units of whole blood in each of the four patients.

Quantitative liver function

The median (interquartile range) value of preoperative MEGX formation was 64.8 ng/ml (56.4 to 83 ng/ml). After the operation, MEGX formation was measured again on the first postoperative day. The median (interquartile range) value of postoperative MEGX formation was 35.8 ng/ml (27 to 54.8 ng/ml). The median (interquartile range) ratio of postoperative MEGX formation to preoperative MEGX formation was 66.1% (44.9% to 85.2%).

Relationship between remnant liver volume and MEGX formation

To assess postoperative liver function to prevent liver failure, we tried to find the relationship between remnant liver volume and liver function. By regression, a linear relationship between the percentage remnant liver volume and ratio of MEGX formation after hepatectomy was found (Fig. 1). The linear regression equation was:

$$\text{(Postoperative MEGX formation/preoperative MEGX formation)} \times 100\% = (0.688 \times \text{percentage of remnant liver volume} + 0.179) \times 100\% \; (r^2 = 0.49) \qquad \text{(Eq. 1)}$$

Because the percentage of remnant liver volume could be estimated preoperatively and the preoperative MEXG formation was already known, postoperative MEXG formation could be calculated.

Relationship between international ratio (INR) of prothrombin time and MEGX formation

Prothrombin time is a sensitive indicator of liver function. To further understand the meaning of the postoperative MEGX level, the relationship between MEGX formation and INR of prothrombin time was determined. By regression, a linear relationship between

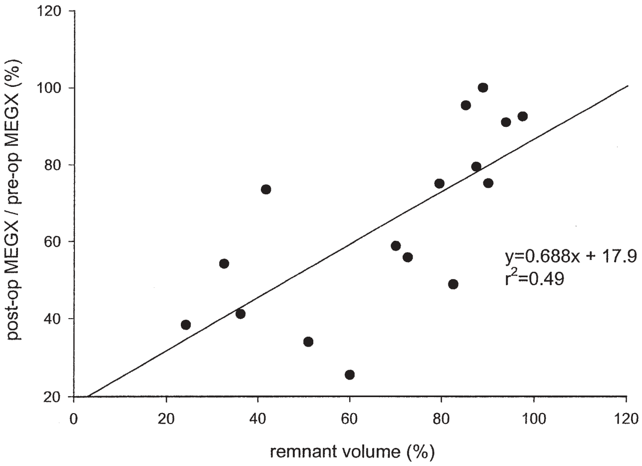

Fig. 1. The relationship between percentage of remnant liver volume and ratio of postoperative monoethylglycinexylidide (*MEGX*) level. A linear relationship was found between the percentage of remnant liver volume and the ratio of the postoperative MEGX level. *Op*, operation

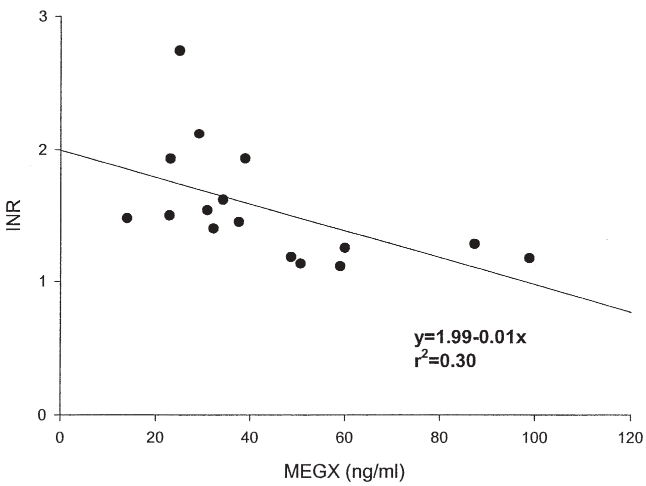

Fig. 2. The relationship between *MEGX* level and international ratio (*INR*) of prothrombin time. The MEGX level has a linear relationship to INR of prothrombin time

MEGX formation after hepatectomy and INR of prothrombin time was found (Fig. 2). The linear regression equation was:

$$\text{INR} = 1.99 - 0.01 \times \text{MEGX}\ (r^2 = 0.30) \qquad \text{(Eq. 2)}$$

Thereafter, when the post-hepatectomy MEGX level was determined, the INR of prothrombin time could be estimated.

MEGX level and post-hepatectomy course

To determine whether the MEGX level could be used to predict the post-hepatectomy course of our patients, the postoperative hospital stay of patients with an MEGX level of less than 30 ng/ml was compared with that of the patients with an MEGX level of 30 ng/ml or more. Excluding one patient with surgical mortality, five patients had an MEGX level of less than 30 ng/ml, and ten patients had an MEGX level of 30 ng/ml or more. The median (interquartile range) duration of postoperative hospital stay for the patients with an MEGX level of less than 30 ng/ml was 20.0 days (18.5 to 23.8 days), which was longer than the 9.0 days (9.0 to 11.0 days) in the patients with an MEGX level of 30 ng/ml or more ($P = 0.003$).

Discussion

Hepatic resection is the first choice of treatment for HCC, and has the best results among the therapeutic options. Along with the progress of surgical techniques, the surgical mortality of hepatic resection is less than 5% currently. However, most surgical mortality occurs in patients with cirrhotic livers, and the incidence of surgical mortality of hepatic resection is as high as 15% in patients with cirrhotic livers.[8–11] How to assess the postoperative functional reserve of a cirrhotic liver preoperatively to prevent hepatic failure is always an important issue in liver surgery. In this study, we demonstrate that the postoperative functional reserve of a cirrhotic liver can be estimated preoperatively by determining quantitative liver function and liver volume. The estimation of postoperative functional reserve can be calculated by the equations shown in this study.

According to the equations we demonstrated in this study, the postoperative MEGX level can be calculated if the parenchymal resection range is decided. According to the MEGX level, the postoperative INR of prothrombin time can also be calculated, and postoperative hospital stay can be estimated. In the literature, some guidelines have been described for a feasible range of hepatic resection in a cirrhotic liver.[12] However, these guidelines can only provide a rough range of parenchymal resection, and cannot indicate the maximal percentage resection of liver parenchyma accurately for an individual patient. The equations in this study can be used to calculate the maximal percentage resection of the parenchyma that will not cause severe liver dysfunction for an individual patient.

Determination of MEGX, formed from the metabolism of lidocaine via oxidative N-deethylation in the liver, is a novel quantitative liver function test. MEGX formation has been used effectively to assess liver function in children,[13] liver donors, and liver transplant recipients.[14] It is also useful for predicting the development of complications in cirrhotic liver diseases,[15–17] and for predicting 1-year pretransplant survival in patients with cirrhosis.[18–20] In this study, we used a MEGX formation value of 30 ng/ml as a cutoff point to examine the postoperative course. The results revealed that the postoperative hospital stay was prolonged if MEXG formation after hepatic resection was less than 30 ng/ml. Huang et al.[21] pointed out that MEGX level was a sensitive indicator of liver dysfunction, and MEGX at 30 ng/ml was a cutoff point to predict patients' survival rate. Arrigoni et al.[17] demonstrated that a MEGX value of 25 ng/ml was a reliable cutoff to discriminate between death and survival in cirrhotic patients. Therefore, MEXG formation can be employed to evaluate liver function quantitatively, and can be used as a short-term prognostic index for patients with hepatic resection.

Computed tomography volumetry was applied to measure liver volume in the present study. Heymsfield et al.[22] have demonstrated that CT can be used to measure liver volume accurately. The difference between radiographic volume and actual volume is only 3% to 5%. Therefore, it is feasible and reliable to use CT scans to measure liver volume, tumor volume, and the volume of the liver expected to be resected, and to calculate the percentage volume of the remnant liver preoperatively. Once the percentage volume of the remnant liver has been calculated, postoperative liver function can be estimated according to Eq. 2 obtained in this study.

In conclusion, an accurate assessment of postoperative liver functional reserve before hepatic resection is very important to prevent posthepatectomy liver failure. The percentage remnant liver volume and a quantitative test of liver function showed a linear relationship, and a linear regression equation was created for remnant liver volume and MEGX formation (Eq. 1). According to this equation, if the percentage parenchymal of resection is set, postoperative liver function can be estimated. In the same way, if a postoperative MEGX level above 30 ng/ml is required, the maximal range of hepatic resection can be determined.

References

1. Chen MF, Hwang TL, Jeng LB, Wang CS, Jan YY, Chen SC (1994) Postoperative recurrence of hepatocellular carcinoma: 205 consecutive patients who underwent hepatic resection in 15 years. Arch Surg 129:738–742
2. Takenaka K, Kawahara N, Yamamoto K, Kajiyama K, Maeda T, Itasaka H, Shirabe K, Nishizaki T, Yanaga K, Sugimachi K (1996) Results of 280 liver resections for hepatocellular carcinoma. Arch Surg 131:71–76
3. Lee WC, Jeng LB, Chen MF (2000) Hepatectomy for hepatitis B-, hepatitis C-, and dual hepatitis B and C-related hepatocellular carcinoma in Taiwan. J Hepatobiliary Pancreat Surg 7:265–269
4. Lee WC, Jeng LB, Chen MF (2002) Estimation of prognosis after hepatectomy for hepatocellular carcinoma. Br J Surg 89:311–316
5. Oellerich M, Raude E, Burdelski M, Schulz M, Schmidt FW, Ringe B, Lamesch P, Pichlmayr R, Raith H, Scheruhn M, Wrenger M, Wittekind C (1987) Monoethylglycinexylidide formation kinetics: a novel approach to assessment of liver function. J Clin Chem Clin Biochem 25:845–853
6. Oellerich M, Armstrong VW (2001) The MEGX test: a tool for the real-time assessment of hepatic function. Ther Drug Monit 23:81–92
7. Okamoto E, Kyo A, Yamanaka N, Tanaka N, Kuwata K (1984) Prediction of the safe limits of hepatectomy by combined volumetric and functional measurements in patients with impaired hepatic function. Surgery 95:586–592
8. Kanematsu T, Takenaka K, Matsumata T, Furuta T, Sugimachi K, Inokuchi K (1984) Limited hepatic resection effective for selected cirrhotic patients with primary liver cancer. Ann Surg 199:51–56
9. Kinami Y, Takashima S, Miyazaki I (1986) Hepatic resection for hepatocellular carcinoma associated with liver cirrhosis. World J Surg 10:294–301
10. Bismuth H, Houssin D, Ornowski J, Meriggi F (1986) Liver resections in cirrhotic patients: a Western experience. World J Surg 10:311–317
11. Fan ST, Lai CS, Lo CM, Ng OL, Wong J (1995) Hospital mortality of major hepatectomy for hepatocellular carcinoma associated with cirrhosis. Arch Surg 130:198–203
12. Yamanaka N, Okamoto E, Oriyama T, Fujimoto J, Furukawa K, Kawamura E, Tanaka T, Tomoda F (1994) A prediction scoring system to select the surgical treatment of liver cancer: further refinement based on 10 years of use. Ann Surg 219:342–346
13. Gremse DA, A-Kader HH, Schroeder TJ, Balistreri WF (1990) Assessment of lidocaine metabolite formation as a quantitative liver function test in children. Hepatology 12:565–569
14. Potter JM, Hickman PE, Lynch SV, Henderson A, Wright M, Balderson G, Strong RW (1993) Use of monoethylglycinexylidide as a liver function test in the liver transplant recipient. Transplantation 56:1385–1388
15. Infante-Rivard C, Esnaola S, Villeneuve JP (1987) Clinical and statistical validity of conventional prognostic factors in predicting short-term survival among cirrhotics. Hepatology 7:660–664
16. Shiffman ML, Fisher RA, Sanyal AJ, Edinboro LE, Luketic VA, Purdum III PP, Raymond P, Posner MP (1993) Hepatic lidocaine metabolism and complications of cirrhosis. Transplantation 55: 830–834
17. Arrigoni A, Gindro T, Aimo G, Cappello N, Meloni A, Benedetti P, Molino GP, Verme G, Rizzetto M (1994) Monoethylglycinexylidide test: a prognostic indicator of survival in cirrhosis. Hepatology 20:383–387
18. Oellerich M, Burdelski M, Ringe B, Lamesch P, Gubernatis G, Bunzendahl H, Pichlmayr R, Herrmann H (1989) Lignocaine metabolite formation as a measure of pre-transplant liver function. Lancet 8639:640–642
19. Oellerich M, Burdelski M, Lautz HU, Binder L, Pichlmayr R (1991) Predictors of 1-year pretransplant survival in patients with cirrhosis. Hepatology 14:1029–1034
20. Oellerich M, Burdelski M, Lautz HU, Rodeck B, Duewel J, Schulz M, Schmidt FW, Brodehl J, Pichlmayr R (1991) Assessment of pretransplant prognosis in patients with cirrhosis. Transplantation 51:801–806
21. Huang YS, Lee SD, Deng JF, Wu JC, Lu RH, Lin YF, Wang YJ, Lo KJ (1993) Measuring lidocaine metabolite-monoethylglycinexylidide as a quantitative index of hepatic function in adults with chronic hepatitis and cirrhosis. J Hepatology 19:140–147
22. Heymsfield SB, Fulenwider T, Nordlinger B, Barlow R, Sones P, Kutner M (1979) Accurate measurement of liver, kidney, and spleen volume and mass by computerized axial tomography. Ann Intern Med 90:185–187