Preoperative Phenacetin Metabolism Test in the Prediction of Postoperative Liver Dysfunction of Patients with Hepatocellular Carcinoma

Authors' Contribution:
Study Design A
Data Collection B
Statistical Analysis C
Data Interpretation D
Manuscript Preparation E
Literature Search F
Funds Collection G

AEF 1 **Xiaohua Pan**
BD 2 **Xiaodong Li**
B 3 **Liqing Cui**
ABC 3 **Qianwei Wang**

1 Department of Operation Room, Huashan Hospital North, Fudan University, Shanghai, P.R. China
2 Cancer Institute, Second Military Medical University, Shanghai, P.R. China
3 Department of General Surgery, Huashan Hospital, Fudan University, Shanghai, P.R. China

Corresponding Author: Qianwei Wang, e-mail: hswangqianwei@126.com
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Background: The risk of postoperative liver dysfunction (PLD) in patients with injured livers, such as in hepatocellular carcinoma (HCC), is still not negligible. Phenacetin metabolism test can reflect hepatic functional reserve in patients with chronic hepatic damage. The aim of this study was to assess the ability of phenacetin metabolism test to predict PLD in patients with HCC receiving partial hepatectomy.

Material/Methods: Forty-nine patients with HCC undergoing partial hepatectomy between 2014 and 2016 were included at Huashan Hospital, Fudan University. The phenacetin metabolism test was used to assess the hepatic functional reserve. The ratio of total plasma paracetamol to phenacetin was collected in patients at 2 h after oral administration of 1.0 g phenacetin, recorded 5 days prior to surgery and on the fifth postoperative day. Phenacetin metabolism test, Child-Pugh classification, and Model for End-Stage Liver Disease (MELD) score were correlated with PLD.

Results: Of 49 patients with HCC, 13 patients (26.5%) had PLD. The association between the ratio of total plasma paracetamol to phenacetin and PLD was statistically significant (p=0.0061) and the correlation coefficient was −0.647 (p=0.0082). The phenacetin metabolism test showed a larger area under the receiver operating characteristic (ROC) curve value (0.735) than Child-Pugh's classification (0.472) and MELD score (0.419). Using the calculated cutoff of 0.6, the lower ratio of total plasma paracetamol to phenacetin preoperatively was chosen to specifically identify patients with PLD. The sensitivity and specificity were 0.657 and 0.892, respectively.

Conclusions: Phenacetin metabolism test could be preoperatively used in predicting PLD in HCC patients receiving partial hepatectomy. It potentially provides better prediction than Child-Pugh classification and MELD score.

MeSH Keywords: Carcinoma, Hepatocellular • General Surgery • Liver Diseases • Liver Function Tests • Phenacetin

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Background

Postoperative liver dysfunction (PLD) can lead to morbidity and mortality after liver resection [1]. In patients with hepatocellular carcinoma (HCC) who undergo extended major hepatectomy, the operative risk is significant and should be carefully evaluated before surgery [2]. The accurate assessment of hepatic functional reserve plays an important role in predicting the risk of PLD [3]. Some assessment tools, such as Child-Pugh classification, Model for End-Stage Liver Disease (MELD) score, and indocyanine green (ICG) test, showed limited value [4]. PLD occasionally occurs in patients with Child-Pugh class A following hepatectomy [5]. For the liver surgeon, it remains a challenge to predict the risk of PLD in HCC patients receiving partial hepatectomy. Careful patient selection and surgical preparation are required for this to be a useful prediction tool before hepatectomy.

A use of a drug to evaluate hepatic functional reserve requires that it is mainly metabolized in the liver and its metabolism is impaired in patients with chronic liver disease. Growing evidence shows phenacetin metabolism test is reliable in the assessment of liver functional reserve in patient with chronic hepatic damage [6–8]. Phenacetin O-deethylation is a marker reaction of cytochrome P4501A2 activity. After the oral administration of phenacetin, its O-deethylated metabolite, paracetamol, is majorly transformed into glucuronide paracetamol or sulfate paracetamol by hepatic UDP-glucuronosyltransferases and sulfotransferase 1A. There was only 3.6% phenacetin in the extrahepatic metabolism [9]. However, little research has been reported about phenacetin metabolism testing in predicting PLD of HCC patients following partial hepatectomy.

In this study, we examined the relationship between preoperative ratio of total plasma paracetamol to phenacetin and PLD in HCC patients receiving partial hepatectomy. Phenacetin metabolism test, Child-Pugh classification, and MELD score were compared in terms of their predictive value for PLD.

Material and Methods

Subjects and materials

From July 2014 to June 2016, 49 patients who had undergone partial hepatectomy for pathologically confirmed HCC at our department were included in this study. All participants provided informed consent. The Ethics Committee of Huashan Hospital, Fudan University approved the study.

Phenacetin was provided by Jiu Zhou Pharmaceutical Co. Ltd. (Shanghai, China). β-glucuronidase and arylsulfatase were obtained from Sigma Chemical Co (St Louis, USA). A Waters X-Terra C18 column purchased from Waters Corporation (Milford, USA) was used in the analysis of HPLC.

Clinical data

Clinical information, including prothrombin time (PT)- international normalized ratio(INR), serum albumin (ALB), total bilirubin (TB), Child-Pugh classification [10], prealbumin (PA), alkaline phosphatase (ALP), alanine aminotransferase (ALT), γ-glutamyl GGT (γ-GT), and procedure type, were collected and recorded. In addition, MELD scores (R) were calculated by the following equation: R=3.8×log (bilirubin mg/dl)+11.2×log (INR)+9.6×log (creatinine mg/dl)+6.4×cause of disease (biliary or alcoholic was 0, and others were 1).

PLD was defined as an abnormal serum bilirubin level and prothrombin time on or after postoperative day 5 by the International Study Group of Liver Surgery [11]. Accordingly, prothrombin time index <75% of normal and serum bilirubin >2 mg/dL(34μmol/L) on postoperative day 5 were classified as PLD at our institution.

Phenacetin metabolism test

Phenacetin metabolism test was performed 5 days prior to hepatectomy as well as on the fifth postoperative day. All patients fasted overnight and received oral administration 1.0 g phenacetin with 200 ml water in the morning. Neither eating nor drinking was allowed for 2 h afterwards. A venous blood sample (2 ml) was collected at 2 h after the intake of phenacetin and was saved at −20°C until required for further use. Before the determination of phenacetin and its metabolites (free-, glucuronide-, and sulfate- paracetamol) by HPLC, β-glucuronidase/arylsulfatases was used for enzymolysis of blood samples at 40°C overnight.

Statistical analysis

All data are presented as means ±SEM and analyzed using SPSS19.0 software. For statistical comparisons, we used the non-parametric Mann-Whitney U test, chi-square test, and *t* test. Pearson correlation coefficient was used in correlation analysis. The predictive ability of phenacetin metabolism testing for PLD was evaluated using the area under the ROC curve. P values <0.05 were considered statistically significant.

Results

There were 43 HCC patients with Child-Pugh class A and 6 HCC patients with Child-Pugh class B in the study. PLD developed in 13 of 49 patients (26.5%), none of whom died. When

Table 1. Comparison of the Characteristic and variable between patients without PLD and those with PLD (mean ±SD).

Characteristic/Variable	Without PLD (n=36)	With PLD (n=13)	P value
Demographic data			
Age (yr.)	50.5±13.2	52.1±11.6	0.7012
Male-female ratio	28: 8	10: 3	0.7456
Body mass index	24.5±3.1	23.4±2.7	0.2634
Laboratory results			
Child-Pugh A/B	34/2	9/4	0.0596
Child-Pugh score	5.3±0.9	5.8±0.6	0.0701
MELD score	7.2±3.3	8.7±2.1	0.1339
PT-INR	1.06±0.18	1.09±0.12	0.5808
TB (µmol/L)	22.9±12.2	25.6±8.3	0.4652
ALB (g/L)	38.7±12.5	42.3±6.9	0.3368
ALT (IU/L)	42.8±62.3	64.7±38.1	0.2419
AST (IU/L)	62.4±58.1	85.2±34.7	0.1910
ALP (IU/L)	86.4±53.2	99.5±46.1	0.4356
γ-GT (IU/L)	53.9±43.5	72.9±38.4	0.1712
PA (g/L)	0.21±0.08	0.19±0.05	0.4047
Pa/Ph	0.67±0.14	0.55±0.09	0.0061
Operative findings			
Operation time (min)	256±94	282±77	0.3763
Tumor size (cm)	2.8±2.2	3.5±1.8	0.3094

MELD score – the model for end-stage liver disease score; PT-INR – prothrombin time–international normalized ratio; TB – total bilirubin; ALB – albumin; ALT – alanine aminotransferase; AST – aspartate aminotransferase; ALP – alkaline phosphatase; γ-GT – γ-glutamyl gamma-glutamyl transferase; Pa/Ph – the ratio of plasma total paracetamol to phenacetin; PLD – postoperative liver dysfunction.

patients with and or without PLD were compared, individuals with PLD were found to exhibit significantly lower ratios of total plasma paracetamol to phenacetin in phenacetin metabolism test preoperatively (p=0.0061). There was no significant difference in demographic data and other laboratory results between patients without PLD and those with PLD, including Child-Pugh classification and MELD score (Table 1). The operation time and tumor size were also not significantly different between the 2 groups.

The potential of preoperative phenacetin metabolism testing to predict PLD was further evaluated. Preoperative phenacetin metabolism test, Child-Pugh classification, and MELD score were analyzed using ROC curves. The area under the curves of phenacetin metabolism test, Child-Pugh classification, and MELD score were 0.735, 0.472, and 0.419, respectively. The

area under the curves of Child-Pugh classification and MELD score both were smaller than that of the phenacetin metabolism test (p<0.05), showing that phenacetin metabolism testing outperformed the Child-Pugh classification and MELD score. Using ROC analysis, a preoperative cutoff level of the phenacetin metabolism test was 0.6, with a sensitivity of 0.657 and a specificity of 0.892 (Figure 1). A preoperative ratio of total plasma paracetamol to phenacetin <0.6 was chosen to specifically identify patients with PLD.

PLD was negatively correlated with the preoperative ratio of total plasma paracetamol to phenacetin (r=−0.647, P=0.0082). Poor positive correlations between PLD and preoperative Child-Pugh classification or MELD score were revealed (Table 2). The postoperative assessment of liver functional reserve in HCC patients receiving partial hepatectomy was further validated. PLD
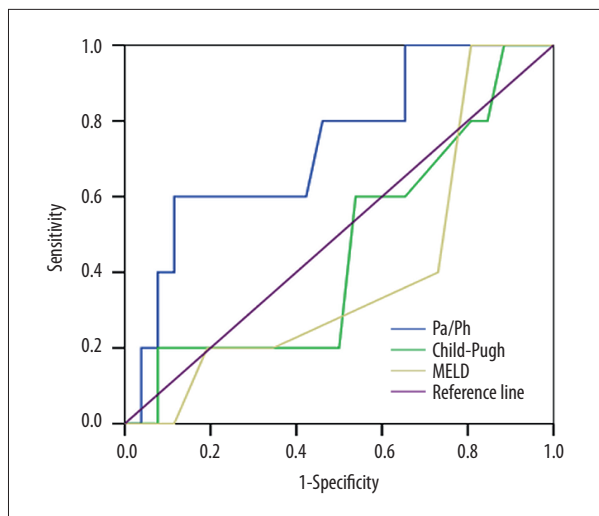
Figure 1. Preoperative phenacetin metabolism test, Child-Pugh classification and MELD score in the prediction of PLD by ROC analysis. Pa/Ph – the ratio of total plasma paracetamol to phenacetin; MELD – model for end-stage liver disease; PLD – postoperative liver dysfunction.

was negatively correlated with the postoperative ratio of total paracetamol plasma to phenacetin (r=−0.693, P=0.0065) and positively correlated with Child-Pugh classification (r=0.560, P=0.0337). However, there was no significant correlation between postoperative MELD score and PLD (Table 3).

Discussion

Hepatectomy is a critical choice in the early stage of HCC. The accurate preoperative assessment of liver functional reserve is important for predicting the risk of PLD. Several studies [12,13] showed that the main cause of mortality in hepatectomy was PLD, although the mortality has been reduced to less than 5% by improving preoperative assessment, perioperative management, and surgical techniques. Thus, a reliable tool for predicting PLD is critical before hepatectomy. In this study, the preoperative phenacetin metabolism test was significantly associated with PLD and can preliminarily identify low-risk patients that are unlikely to develop PLD.

The definition of PLD has been under debate during the past few years. The incidence of PLD in the literature varies between 1.2% and 32%. Thus, the International Study Group of Liver Surgery made great effort to define a clinically relevant criterion to reflect PLD in patients undergoing liver resection [11]. In this study, we optimally defined PLD according to these criteria, finding that PLD was present in 13 cases (26.5%). Preoperative phenacetin metabolism testing can predict PLD, thereby demonstrating its clinical relevance.

Table 2. Correlation between several preoperative parameters and PLD in HCC patients.

Related pairs	Correlation index	P-value
Pa/Ph: PLD	−0.647	0.0082
Child-Pugh: PLD	0.385	0.0899
MELD: PLD	0.292	0.1328

Preoperative – five days prior to hepatectomy; Pa/Ph – the ratio of plasma total paracetamol to phenacetin; MELD – the model for end-stage liver disease; PLD – postoperative liver dysfunction.

Table 3. Correlation between several postoperative parameters and PLD in HCC patients.

Related pairs	Correlation index	P-value
Pa/Ph: PLD	−0.693	0.0065
Child-Pugh: PLD	0.560	0.0337
MELD: PLD	0.477	0.0762

Postoperative – on the fifth postoperative day; Pa/Ph – the ratio of plasma total paracetamol to phenacetin; MELD – the model for end-stage liver disease; PLD – postoperative liver dysfunction.

Conventional biochemical tests, Child-Pugh classification, MELD score, and ICG test are usually involved in the preoperative evaluation of hepatic functional reserve. However, the accuracy and reliability of these methods are barely satisfactory. If surgery is selected as the method of treatment based on the Child-Pugh classification, the risk for PLD is likely to increase [14]. Some studies have suggested that there is no significant correlation between the MELD score and PLD [15,16]. A previous study also showed that the predictive value of ICG retention testing in high-risk patients with PLD was unable to be documented [17]. ICG clearance can be affected by postoperative hemodynamics. In our study, phenacetin metabolism test showed better prediction of PLD in HCC patients than did Child-Pugh classification and MELD score. Calculating the cut-off point <0.6, the ratio of total plasma paracetamol to phenacetin indicated positive predictive value in predicting PLD with high specificity.

Quantifying PLD remains a difficult task in liver resection, and classical liver function parameters might be largely affected by the intra-operative course. In China, most HCC results from HBV infection [18]. In HCC patients with Child-Pugh class A, the impairment in liver function is often not reflected in the classification. In this study, Child-Pugh classification on postoperative day 5 seems to represent a useful parameter to identify

patients with PLD, but preoperative Child-Pugh classification cannot. However, phenacetin metabolism test 5 days prior to surgery, as well as on the fifth postoperative day, was found to be strongly associated with PLD, demonstrating the lower utility of Child-Pugh classification in evaluating liver functional reserve, which is in accordance with previous reports [6].

Main limitations to this study are: the small number of patients; other clinical measurements such as ICG retention test (ICG15) were not included and we were unable to assess the prediction of phenacetin metabolism test as compared with them; and the time-consuming assessment for phenacetin metabolism test needs to be improved. Further studies with lager sample sizes are needed to validate its capacity to predict PLD in HCC patients after partial hepatectomy.

Conclusions

Phenacetin metabolism test can be used preoperatively in predicting PLD in HCC patients receiving partial hepatectomy. It is likely to provide better prediction than Child-Pugh classification and MELD score. Phenacetin metabolism test may be a useful clinical tool to distinguish low- and high-risk patients with PLD who require evaluation and close monitoring. With this prediction tool, we may be able to improve the surgical procedures and enhance the reasonable choices of patients to reduce the incidence of PLD.

Conflict of interest

The authors declare that they have no conflicts of interest.

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