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Evaluation indices of hepatitis-related hepatic cirrhosis and their relations to postoperative awakening time

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Abstract

Objective: To investigate the anesthesia-postoperative awakening time (AT) of hepatitis-related cirrhosis patients and their relations to grading scores, portal venous pressure (PVP), prealbumin (PA), and age, to predict postoperative AT and provide a basis for adjustment of anesthetic doses during operation.

Methods: A total of 71 patients with hepatic cirrhosis and hypersplenism at ASA grade I to II were subject to splenectomy and gastric cardia devascularization under total intravenous anesthesia. The depth control of anesthesia (MAP±20% base value; BIS40-60) and the monitoring of muscular relaxation were taken by HXD-I multifunctional quantitative electroencephalogram monitor. Child-Turcotte-Pugh (CPT) and Model for end-stage liver disease (MELD) scoring were carried out prior to operation so that intraoperative PA and PVP as well as postoperative extubation time (ET) and AT were determined.

Results: Both ET and postoperative recovery time of the cirrhosis group were significantly longer than those of the non-cirrhosis group ($P<0.05$). There was a linear relationship between each two variables ET and AT ($r=0.962$, $P<0.001$). After the stepwise regression, variables of CTP, PA and PVP were assigned into the regression equation as $AT= -39.7+ 8.3\times CTP+0.79\times PVP-78.57\times PA$ (the multiple correlation coefficient $r=0.942$, the coefficient of determination $r^2=0.887$, and the corrected coefficient of determination $r^2=0.882$; $F=176.007$), ($P<0.001$). The standard partial regression coefficients of CTP, PA and PVP were 0.460, 0.303 and -0.217, respectively.

Conclusion: The anesthesia-postoperative AT of hepatitis-related cirrhosis patients is most closely related to CTP, PVP and PA (CTP > PVP > PA). The anesthesia-postoperative AT can be calculated with the following formula: $AT= -39.7+8.3\times CTP+0.79\times PVP-78.57\times PA$.

Keywords: hepatic cirrhosis, awakening time, CTP scoring, MELD scoring, Prealbumin, portal venous pressure; total intravenous anesthesia

Introduction

Suffering from a reduction of functional liver cells, the cirrhosis patient generally has a reduced metabolism ability of liver cells for endogenous compounds and exogenous drugs. Severe hepatic cirrhosis is often complicated with multiple system dysfunctions over the whole body, and the risk of anesthesia is fairly high. Anesthesia may lead to a secondary hepatic coma especially after prolonged and major surgery and the postoperative awakening time (AT) extend significantly compared to non-cirrhotic patients [1,2]. However, the postoperative AT is affected by a variety of factors. In addition to the fact that the anesthesia reduces the liver cells' ability to metabolize and secrete

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drugs or reduces the blood flow in the liver, the effect of liver function on postoperative AT has been paid more and more attention. In the present study, the anesthesia-postoperative AT of the hepatitis-related cirrhosis patients and their relations to grading scores (CTP and MELD), portal venous pressure (PVP), prealbumin (PA), and age were investigated to predict the postoperative AT and provide basis data for the adjustment of anesthetic doses during operation.

Methods

Subjects

With ethics committee approval from the Affiliated hospital of the Ningxia Medical College, Yinchuan, People's Republic of China, and written informed consent,71 patients hospitalized from October 2005 to June 2007 in our hospital were chosen in whom hepatic cirrhosis and hypersplenism were diagnosed clinically. 28 of them still suffered from upper gastrointestinal bleeding. In addition to symptomatic and supportive treatment, all of them were subject to splenectomy as well as gastric cardia devascularization. Another 30 non-cirrhotic patients underwent laparotomy; for these patents, no icterus was observed and the liver function, the proteins and the clotting time were normal. Patients ranged in age from 18 to 60 years, weighed from 45 to 90 kg, and were 150 to 180 cm tall. The general information is shown in Table 1.

Anesthesia and monitoring

All patients fasted overnight and were restricted from oral intake of clear fluid for two to three hours. They were all normothermic. Midazolam 0.1 mg/kg and scopolamine 0.01 mg/kg (maximum, 0.3mg) were given intramuscularly one hour before anesthesia. After entering the operation room, each patient was subject to IV access via an 18G needle at the ankle veins, and then intravenous anesthetics were given. The mean arterial pressure (MAP) was monitored by using an invasive blood pressure monitor (Philips, MP20) after anesthesia. The bispectral spectrum index (BIS), heart rate (HR), saturation of blood oxygen (SpO_2), partial pressure of carbon dioxide in end expiratory gas ($PetCO_2$) were monitored using HXD-I monitor (Harbin Huaxiang Company). The ulnar nerve stimulation was conducted for the monitoring of muscular relaxation, to determine the myopalmus response of adductor pollicis; the train-of-four stimulation (TOF) was taken as the stimulating mode. 0.04mg/kg of midazolam, 3μg/kg of fentanyl, 0.75mg/kg of atracurium, and 1mg/kg of propofol (1% Diprivan) was used for the induction of anesthesia by rapid endotracheal intubation connecting to the anesthetic machine at 1L/min of oxygen flow rate. The continuous intravenous pump-infusion of propofol (Astra Zeneca, Italy; Lot number CP931) was then conducted by using the Diprifusor/TCI system (Craseby Medical, UK) with the internal setting of Marsh pharmacokinetic parameters, while that of remifentanil

General information	The cirrhosis group	The non-cirrhosis group
Male/female (cases)	45/26	21/9
Average age (years old)	38.4±8.7	42.1±12.6
Average body weight (kg)	60.0±14.2	62±15.1
Average time of anesthesia (min)	182.5±42.1	171.5±40.4
Average time of operation (min)	152.9±26.3	132.7±22.4
Average time of extubation (min)	20±8.6*	11±3.5
Average time of postoperative recovery (min)	27.1±11.7*	15±4.8

* $P<0.001$, as compared between the above two groups.

Table 1. General information of subjects.

(Hubei Yichang Renfu, China; Lot number 04051) by using the Type I TCI system (Beijing Silugao, China) with the internal setting of Minto pharmacokinetic parameters. According to the observations of Miline et al [3] and Quattara et al [4], the target levels of propofol and remifentanil in the plasma were 2.5 to 3.5 μg/ml and 2.5 to 3.5ng/ml, respectively. The micropump infusion of atracurium was conducted at a rate of 5 to 10μg/kg/min. TOF neuromuscular monitoring was undertaken. 30 min prior to the end of surgery, the infusion of atracurium was stopped, and 1μg/kg of fentanyl was administered to relieve postoperative pain. 10 min prior to the end of surgery, the infusion of propofol and remifentanil was stopped. Postoperative TOF stimulation was conducted; once one myopalmus response was observed, 0.02mg/kg of atropine and 0.04mg/kg of neostigmine were administrated to antagonize the residual muscular relaxation. During operation, a $PetCO_2$ of 35 to 45 mmHg (4.5 to 6 kPa) was supplied at room temperatures of 22 to 25°. The estimated blood loss was less than 500 ml.

Control by depth of general anesthesia

The MAP was maintained to be the base value ± 20%, while the BIS was kept between 40 to 60; if below or above the above two ranges, the pump-infusion of propofol and remifentanil should be increased or decreased, respectively. If the HR was less than 55 beats/min, the above pump-infusion speeds would be slowed down.

Extubation

The extubation was undertaken only if the T4/T1 ratio was larger than 0.75, and the tidal volume (VT) was larger than 6ml/kg, and the respiratory frequency (Rf) was greater than 12 breaths/min, and both swallowing and bucking reflexes recovered.

Monitoring of liver function

-Diagnosis of cirrhosis and ascites

The cirrhosis and ascites were diagnosed on the basis of clinical symptoms, physical signs, liver B-type ultrasound (diffuse changes, enhanced and thickened echoes of hepatic parenchyma, non-smoothness on the liver surface, blunt edges of liver, enlarged spleen, granular liver surface, nodular changes in hepatic parenchyma, and fluidity dark regions in abdominal cavity), and the intraoperative conditions of liver surface and ascites observed by naked eyes.

-CPT scoring [5]

Each of the five indices, including two biochemical indices (bilirubin and albumin), prothrombin time, clinical symptoms (encephalopathy) and whether there was intraoperative ascites, was counted as grade 1, 2 or 3. The score of five indices were summed for each patient.

-MELD scoring [6]

The international normalized ratio, serum total bilirubin, serum creatinine and prothrombin time as well as the etiological rating constituted the formula, the MELD score = 3.8 × log [bilirubin (mg/dl)] +11.2 × log (INR) +9.6 × log [creatinine (mg/ml)] +6.4 × (etiological factor: 0 for biliary or alcoholic, and 1 for the others).

-Determination of PVP

The PVP was determined by cannulation of the right gastroepiploic vein.

-Preoperative detection of PA

The PA was determined by the immunoturbidimetry (ITM) method.

Determination of postoperative ET

The ET referred to the time from the end of surgery to the removal of the endotracheal tube.

Determination of postoperative AT

After the operation, the Modified Observer's Assessment of Alertness/Sedation scale (MOA A/S) was conducted to score, and the preoperative time to reach score 5 was measured (score 5: responds readily to name spoken in normal tone).

Variable	Mean	Std. deviation	n
CTP (score)	6.7	0.7	71
MELD (score)	6.2	2.1	71
PA (g/L)	0.13	0.03	71
PVP (cmH_2O)	28.2	4.5	71
AGE (y)	39.1	8.3	71
ET (min)	20.0	8.6	71
AT (min)	27.1	11.7	71

Table 2. Descriptive statistics.

Statistical analysis [7]

The SPSS software 10.0 was used for data analysis. Each data value was expressed with mean ± standard deviation. The correlation coefficient as well as the equation was calculated by using the multiple linear regression analysis. A P value less than 0.05 was considered to be statistically significant.

Results

General information

A total of 71 cirrhosis patients including 45 males and 26 females, aged 38.4±8.7yr. and weighing 60±14.2 kg.were analyzed (the cirrhosis group). The cirrhosis was diagnosed clinically at the grade of ASA I to II. An additional 30 non-cirrhosis patients (21 males and 9 females) at the ASA grade of I to II were also included (the non-cirrhosis group). For weight, anesthesia time and operation time, there was no statistically significant difference between the two groups (P>0.05). Both extubation and postoperative recovery times of the cirrhosis group was significantly longer than those of the non-cirrhosis group (P <0.05; Table 1).

Average values, standard deviation and case numbers of AT, ET,CTP, MELD, PA, PVP and AGE are shown in Table 2.

There was a linear relationship between each two variables of ET and AT (r=0.962, P<0.001).

Both dependent variable (AT) and independent variables (CTP, MELD, PA, PVP and AGE) met a normal distribution.

The stepwise regression of AT against CTP, MELD, PA, PVP and AGE generated a regression model as shown in Table 3.

After the above stepwise regression, the results of variance analysis are shown in Table 4.

After the above stepwise regression (Criteria: Probability-of-F-to-enter <= 0.050, Probability-of-F-to-remove >= 0.100), the regression equation and the regression coefficients and tests were shown in Table 5.

AT= -39.7+8.3×CTP+0.79×PVP-78.57×PA (the multiple correlation coefficient r=0.942, the coefficient of determination r^2=0.887, and the corrected coefficient of determination r^2=0.882; F=176.007, P<0.001).

Model	R	R Square	Adjusted R square	Std. error of the estimate
1	0.922[a]	0.85	0.848	4.575
2	0.937[b]	0.878	0.874	4.167
3	0.942[c]	0.887	0.882	4.028

a. Predictors: (constant), CPT
b. Predictors: (constant), CPT, PVP
c. Predictors: (constant), CPT, PVP, PA
d. Dependent variable: AT

Table 3. Model summary[d].

Model		Sum of squares	df	Mean Square	F	Sig
1	Regression	8210.426	1	8210.426	392.358	0.000[a]
	Residual	1443.884	69	20.926		
	Total	9654.31	70			
2	Regression	8473.097	2	4236.548	243.889	0.000[b]
	Residual	1181.213	68	17.371		
	Total	9654.31	70			
3	Regression	8567.227	3	2855.742	176.007	0.000[c]
	Residual	1087.083	67	16.225		
	Total	9654.31	70			

a. Predictors: (constant), CPT
b. Predictors: (constant), CPT, PVP
c. Predictors: (constant), CPT, PVP, PA
d. Dependent variable: AT

Table 4. ANOVA[d]

The formula [8]

y=B0+B1X1+B2X2+…BpXp, where y was estimated value of the average dependent variables under the condition that a fixed value was given to each independent variable, and X1, X2,…Xp were independent variables, and p was the number of independent variables, and B0 was the constant term of the regression equation (also called intercept), while B1, B2, … Bp were called the partial regression coefficients.

Conclusion

Hepatic cirrhosis complicated with esophageal variceal bleeding is a common cause of death for the hepatic cirrhosis patient; this disease is very dangerous, with a high fatality rate. Splenectomy and esophageal and gastric vein devascularization can greatly reduce the fatality rate due to upper gastrointestinal bleeding in hepatic cirrhosis patients. The preoperative support therapy, such as liver protection and rectification of electrolyte disorder, of the hepatic cirrhosis patients can somewhat reduce the risks of anesthesia. However, the reduction of liver function in the hepatic cirrhosis patient is a chronic process, which has still a big difference compared to the non-hepatic-cirrhosis patient; additionally, surgical trauma, various stress responses triggered by anesthesia, and re-

Model		Unstandardized coefficients		Standardized partial coefficients	t	Sig.
		B	Std. error	Beta		
1	(Constant)	-83.320	5.601		-14.876	0.000
	CTP	16.576	0.837	0.922	19.808	0.000
2	(Constant)	-70.729	6.043		-11.704	0.000
	CTP	10.596	1.716	0.590	6.175	0.000
	PVP	0.965	0.248	0.371	3.889	0.000
3	(Constant)	-39.657	14.161		-2.800	0.000
	CTP	8.263	1.921	0.460	4.302	0.000
	PVP	0.788	0.251	0.303	3.140	0.000
	PA	-78.570	32.620	-0.217	-2.409	0.000

a. Dependent variable: AT

Table 5. Coefficient[a].

duction in liver blood flow further reduces liver function in hepatic cirrhosis patients. As a result, their capability of metabolizing and clearing anesthetics decrease significantly, potentially leading to the prolongation of postoperative AT. Data presented here showed the twofold extension of both postoperative ET and AT. The difference in anesthesia and administration as well as the injury of the central nervous system could be excluded from the reasons to cause the above extension, and moreover the transfusion, the amount of bleeding and the end expiratory $PetCO_2$ were controlled within a certain level. Therefore, it could be considered that the postoperative ATs' of the hepatitis-related cirrhosis patients were closely related to liver function. We still performed the multiple stepwise regression analysis of the above postoperative AT against CTP score, MELD score, PVP, PA and age. Only CPT, PVP and PA were introduced in the regression equation ($AT=-39.7+8.3\times CTP+0.79\times PVP-78.57\times PA$), indicating that the postoperative AT was most closely related to CPT, PVP and PA. Multiple stepwise regression is one of the methods for multiple regression analysis [6]; the principles are as follows: the interdependence between the various factors, as well as the size and direction of action of each factor on the regression results, will be evaluated; for the P independent variables in the regression equation, some of them separately has the effect on the dependent variable Y (closely related), while these P independent variables affect each other; during the regression analysis, their effects on the dependent variable will be probably replaced by those of other independent variables, thus making them to be of little importance in the regression equation; at this time, the retention of these independent variables in the regression equation will not only increase statistical conflict, but cannot guarantee good regression results; multiple stepwise regression can overcome the above shortcomings; the multiple stepwise regression includes only the independent variables having significant effect on the dependent variables, so as to build the optimal regression equation. As shown by the significance test on the standard partial regression coefficient and the partial regression coefficient, the affects of the three on AT were as follows: CTP> PVP> PA, while MELD score and age were not closely related to AT. All of the CTP score, PVP and PA are able to reflect the reservation state of liver function, and also can be used for the prediction of surgical mortality [9]. The MELD score, combining with the kidney function, is a continuous scoring system; it is able to give a detailed description of the severity of the patient's condition; it has a good correlation with the severity of liver disease [10]. The older the ages were, the longer the recovery time would be. However, the cirrhosis patients analyzed in the present study had a normal range of liver creatinine, and moreover no elderly patients were included, which may have accounted for the results that both MELD score and age did not play an important role in the regression equation. In addition, the exogenous or endogenous compounds can be removed by the biological conversion or by the secretion of prototypes of these compounds into bile. The clearance of drugs in the liver is affected by a variety of factors; the most important ones are the changes in the liver blood flow into liver cells, as well as the biological conversion and secretory functions of liver cells, while other factors include the drug binding function, i.e, the ratio of free drugs relative to the tuberculosis drugs, and the distribution volume of drugs [11]. Weng et al reported [12] that the decrease in the plasma protein concentration resulted in the increased concentration of free drugs in the blood, thus enhancing the action of drugs, and thereby leading the left shift of the vecuronium dose-effect relationship curve; with a significantly prolonged time of action of the drugs. The half-life of PAB in the serum is 1.9 days, greatly shorter than that (21 days) of ALB. Therefore, the ALB can more sensitively reflect the damage of liver parenchyma during the acute pathological changes in the liver, as well as the degrees of damage in the liver [9]. However, for the patients with cirrhosis complicated with ascites, both the low protein and portal hypertension will last for a long time, and recur again and again; the body has evolved certain adaptability to this. For the patients with liver dysfunction, the ability to remove drugs depends on the absorption, processing and distribution of drugs. The processing of drugs by the liver is dependent of the blood flow in the liver and the metabolic ability of liver cells, in addition to the patients' sensitivity to drugs.

In summary, the anesthesia-postoperative AT of the hepatitis-related cirrhosis patient is closely related to CTP, PVP and PA (CTP>PVP>PA). The anesthesia-postoperative AT can be calculated with the following formula: AT=-39.7+8.3×CTP+0.79×PVP-78.57×PA.

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