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Related Factors of Jaundice Reduction Effect in Patients with High Biliary Obstruction Caused by Hilar Cholangiocarcinoma Using Endoscopic Retrograde Cholangiopancreatography

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1. Abstract

1.1. Background: The purpose of this study was to explore the risk factors of poor jaundice reduction effect in patients with high biliary malignant obstruction (HBMO) caused by unresectable hilar cholangiocarcinoma (u-HC) treated with endoscopic retrograde cholangiopancreatography (ERCP).

1.2. Methods: Total of 39 cases were retrospectively reviewed from March 2016 to January 2022. We analyzed the effects of age, gender, the level of alpha fetoprotein, carcinoembryonic antigen, carbohydrate antigen 125, carbohydrate antigen 199, albumin, alanine transaminase, aspartate aminotransferase, alkaline phosphatase, gamma glutamyltranspeptidase, cholinesterase, total bile acids, total bilirubin, direct bilirubin, indirect bilirubin and prothrombin pre-ERCP, the highest value of amylase, white blood cell count, C-reactive protein and temperature post-ERCP, longest stricture length, Bismuth type, sphincterotomy status, intra-hepatic dissemination, gallstones, unilateral/bilateral drainage and percutaneous transhepatic biliary drainage on jaundice reduction effect. The decrease of TB and DB both by 20% was considered to be good jaundice reducing effect during the first endoscopic treatment process.

1.3. Results: The total effective rate was 59.0% (23/39). We found that the proportion of patients complicated with intra-hepatic dissemination in the jaundice-reducing ineffective group was significantly higher than that in the jaundice-reducing effective group (81.3% *vs.* 34.8%, $p<0.05$). Binary Logistic Regression analyses showed that intra-hepatic dissemination was the only factor associated with poor jaundice reducing effect (hazard ratio: 8.125, 95% confidence interval: 1.776-37.172, $p<0.05$).

1.4. Conclusion: ERCP was an effective way to reduce jaundice in u-HC patients with HBMO. Combination with intra-hepatic metastasis was a risk factor for the decline of the success rate of jaundice reduction.

2. Introduction

HBMO is usually a lethal condition caused by hilar cholangiocarcinoma, intra-hepatic cholangiocarcinoma, icteric type hepatoma, locally advanced tumor growth such as gastric cancer, metastatic hilar lymph nodes or intra-hepatic metastases from remote cancer [1,2]. Most patients with HBMO have lost the chance of radical surgery and have limited life expectancy with a less than 10% five-year survival, accompany with distressing symptoms, such as intractable pruritus [3,4]. Currently, ERCP biliary drainage (ERCP-BD) is the intervention of choice in patients with HBMO (especially non-resectable HBMO) with a low complication [5]. Besides improving quality of life (such as free patients from pruritis), it also prolong life by decreasing hyperbilirubinemia so as to surgery or chemotherapy. ERCP-BD has been used for several decades. However, the optimal endoscopic approach to the drainage of HBMO remains controversial [6-17]. Furthermore, there are few articles to focus the related

factors of drainage effectiveness during endoscopic drainage of HBMO caused by u-HC. The retrospective study is to explore the risk factors of poor jaundice reduction effect in u-HC patients with HBMO treated by ERCP.

3. Materials and Methods

This single-center retrospective study was conducted at the Shulan (Hangzhou) Hospital, Affiliated to Shulan International Medical College, Zhejiang Shuren University, P.R. China. The study protocol was approved by ethic committees of the Shulan (Hangzhou) Hospital. HBMO was classified into four types using Bismuth classification [18]. The diagnosis of malignant disease was based on percutaneous color doppler ultrasound biopsy of liver mass pathological diagnosis (N=7), ERCP cell brush detection of adenocarcinoma cells (N=13), and imaging examination to indicate u-HC with invasion of surrounding tissues or intra-hepatic metastasis (N=19). The inclusion criteria were: ERCP procedures were performed in our hospital and the patients' age was ≥ 18 years. The exclusion criteria: high bile duct obstruction with common bile duct stones or intra-hepatic bile duct stones; history of ERCP in other hospitals, and patients who were treated with artificial liver support system before or after ERCP. The decrease of TB and DB both by 20% was considered to be good jaundice reducing effect (the latest serum TB and DB measured before discharge divided by the latest serum total TB and DB values before ERCP). We analyzed the effects of age, gender, the level of Alpha fetoprotein [AFP] (0-20ng/ml), Carcinoembryonic antigen [CEA] (0-5ng/ml), Carbohydrate antigen 125 [CA125] (0-35u/ml), Carbohydrate antigen 199 [CA199] (0-37u/ml), albumin [ALB] (35-55g/l), gamma glutamyltranspeptidase [γ-GGT] (10-50U/L), alkaline phosphatase [AKP] (40-150U/L), total bile acids [TBA] (0.5-10umol/L), prothrombin [PT] (9.4-12.5s), alanine transaminase [ALT] (5-40U/L), aspartate aminotransferase [AST] (15-40U/L), cholinesterase [CHE] (5100-11700U/L), total bilirubin [TB] (0-21umol/L), direct bilirubin [DB] (0-5umol/L), indirect bilirubin [IB] (3-14 umol/L) before ERCP, the highest level of amylase (35-135 U/L), white blood cell count [WBC] (3.5-9.5 10E9/L), C-reactive protein [CRP] (0-10mg/L) and temperature (℃) post ERCP, sphincterotomy status, gallstones, longest stricture length (the length of stricture was measured by comparing with the transverse diameter of duodenoscopy), intra-hepatic dissemination, unilateral/bilateral drainage, PTBD and biliary drainage time (hospital stay from first ERCP-BD procedure to discharge) on jaundice reduction in u-HC patients with HBMO. Only PTBD drainage or nasobiliary drainage, and a plastic / metal stent implement was taken as unilateral drainage. One side of plastic stent, the other side of metal stent, one side of PTBD, the other side of plastic / metal stent, both sides of the plastic stent were taken as bilateral drainage. All ERCP operations were performed by professional endoscopists with endoscopic nurses using Olympus duodenoscope (JF-240/TJF-260, Olympus Optical Co., Ltd., Tokyo, Japan). Moderate and deep sedation was used under the premise of ensuring patient safety. The patients with pathological diagnosis of u-HC were followed up for at least 1 month, and the patients with clinical diagnosis were followed up for at least 3 months. Chi square test was used to evaluate the difference of categorical variables between two groups. Independent Students' T-test and Mann-Whitney U test were used to compare the difference of continuous variables between two groups. Risk factors were assessed by Binary Logistic regression. The level of statistical significance for all the tests was defined as $P < 0.05$.

4. Results

The jaundice-reducing effective rate in total patients was 59.0% (23/39). A total of 27 ERCP procedures were performed in the jaundice-reducing effective group, and 18 ERCP procedures in the jaundice-reducing ineffective group. There were no severe complications such as intestinal perforation, severe acute pancreatitis or massive bleeding caused by the ERCP-BD. There were no significant differences in the age, tumor markers, liver function indexes, PT, biliary drainage time, stricture length or the highest value of WBC between the jaundice-reducing effective group and the jaundice-reducing ineffective group ($p>0.05$), as shown in (Table. 1). Unexpectedly, the level of CRP post ERCP-BD was slightly higher in the jaundice-reducing effective group than in the ineffective group (58.4 *vs.* 49.9 mg/L). Likely, the temperature and the rate of patients with maximum body temperature exceeding 38℃ post ERCP-BD was slightly higher in the jaundice-reducing effective group than in the ineffective group, too (38.1 *vs.* 37.8℃, 0.52 *vs.* 0.31, respectively). We found that the proportion of patients combined with intra-hepatic dissemination in the jaundice-reducing ineffective group was significantly higher than that in the jaundice-reducing effective group (81.3% *vs.* 34.8%, $p<0.05$), as shown in (Table. 2). However, there were no differences in the other classification variables between the two groups ($p>0.05$). What's more, Binary Logistic Regression analyses showed that intra-hepatic dissemination was the only factor associated with poor jaundice reducing effect [hazard ratio (HR): 8.125, 95% confidence interval (CI): 1.776-37.172, $p<0.05$) (Table. 3).

Table 1: Structure length or the highest value of WBC between the jaundice-reducing effective group and the jaundice-reducing ineffective group

	Total patients	jaundice-reducing effective group	jaundice-reducing ineffective group	*P* value
age (years)	71.2 ± 11.8	70.2 ± 11.6	72.6 ± 12.2	> 0.05
pre-ERCP ALB (35-55g/L)	34.1 ± 4.1	33.7 ± 4.3	34.7 ± 3.8	> 0.05
pre-ERCP AFP (0-20ng/ml)	9.7(2.4)	11.6(2.4)	7.2(3.0)	> 0.05
pre-ERCP CEA (0-5ng/ml)	38.5(7.7)	14.0(7.8)	70.6(10.2)	> 0.05
pre-ERCP CA125 (0-35u/ml)	133.6(131.2)	161.0(152.4)	99.4(62.4)	> 0.05
pre-ERCP CA199 (0-37u/ml)	3015.0(5228.0)	3746.0(7917.9)	2055.0(2422.7)	> 0.05
pre-ERCP GGT (10-50U/L)	499.4 ± 395.9	508.0 ± 433.0	486.9 ± 348.8	> 0.05
pre-ERCP AKP (40-150U/L)	399.4 ± 237.7	381.8± 222.8	424.8 ± 263.0	> 0.05
pre-ERCP TBA (0.5-10umol/L)	159.4 ± 98.7	170.7 ± 97.0	144.9 ± 102.7	> 0.05
pre-ERCP PT (9.4-12.5s)	12.7 ± 1.8	12.7 ± 1.6	12.8 ± 2.1	> 0.05
pre-ERCP TB (0-21umol/L)	233.2 ± 128.8	212.3 ± 106.5	263.2 ± 154.2	> 0.05
pre-ERCP DB (0-5umol/L)	186.1 ± 103.1	170.3 ± 87.9	208.9 ± 121.1	> 0.05
pre-ERCP IB (3-14 umol/L)	44.5 ± 32.3	37.7 ± 27.1	54.3 ± 37.3	> 0.05
pre-ERCP ALT (5-40U/L)	130.4 ± 122.3	130.6 ± 128.1	130.1 ± 117.5	> 0.05
pre-ERCP AST (15-40U/L)	118.5 ± 87.2	114.5 ± 90.8	124.3 ± 84.2	> 0.05
pre-ERCP CHE (5100-11700U/L)	4340.0 ± 1438.5	4396.0 ± 1441.6	4262.0 ± 1489.2	> 0.05
post-ERCP WBC (3.5-9.5 10E9/L)	10.5 ± 5.4	10.3 ± 3.9	10.7 ± 7.2	> 0.05
post-ERCP CRP (0-10mg/L)	55.2 ± 48.8	58.4 ± 51.8	49.9 ± 44.8	> 0.05
post-ERCP temperature (˚ C)	38.0 ± 0.8	38.1 ± 0.8	37.8 ± 0.9	> 0.05
post-ERCP amylase (35-135 U/L)	404.7(562.0)	435.0(559.0)	361.1(566.3)	> 0.05
stricture length (cm)	2.5 ± 1.2	2.3 ± 1.0	2.8 ± 1.4	> 0.05
drainage time (days)	14.1 ± 9.9	15.8 ± 7.0	11.6 ± 12.9	> 0.05

Table 2: The jaundice-reducing ineffective group was significantly higher than that in the jaundice-reducing effective group

	Total patients	jaundice-reducing effective group	jaundice-reducing ineffective group	*P* value
male (%)	61.5	60.9	62.5	> 0.05
sphincterotomy (yes, %)	66.7	60.9	75.0	> 0.05
drainage mode (bilateral, %)	53.8	60.9	43.8	> 0.05
PTBD (yes, %)	28.2	30.4	25.0	> 0.05
Bismuth type				> 0.05
I	2.6	4.3	0	
II	15.4	21.7	6.3	
III	5.1	8.7	0	
IV	76.9	65.2	93.8	
gallstone (yes, %)	41.0	39.1	43.8	
intrahepatic dissemination (yes, %)	53.8	34.8	81.3	< 0.05

Table 3: Binary Logistic Regression analyses showed that intra-hepatic dissemination was the only factor associated with poor jaundice reducing effect

	Binary Logistic Regression		
Variables	*P* value	HR	95% CI
age	> 0.05	/	/
pre-ERCP PT	> 0.05	/	/
pre-ERCP TB	> 0.05	/	/
pre-ERCP DB	> 0.05	/	/
pre-ERCP IB	> 0.05	/	/

pre-ERCP ALT	> 0.05	/	/
pre-ERCP AST	> 0.05	/	/
pre-ERCP CHE	> 0.05	/	/
post-ERCP WBC	> 0.05	/	/
post-ERCP CRP	> 0.05	/	/
post-ERCP temperature	> 0.05	/	/
post-ERCP amylase	> 0.05	/	/
gender	> 0.05	/	/
sphincterotomy	> 0.05	/	/
drainage mode	> 0.05	/	/
PTBD	> 0.05	/	/
Bismuth type	> 0.05	/	/
gallstone	> 0.05	/	/
intrahepatic dissemination (yes, %)	< 0.05	8.125	1.776-37.172
ERCP: endoscopic retrograde cholangiopancreatography; HR: hazard ratio; 95% CI: 95% confidence interval			

5. Discussion

HBMO, the thorny problem in clinic work (mainly caused by u-HC, intra-hepatic cholangiocarcinoma and metastatic liver cancer) inducing various pathophysiological disorders, such as the liver, kidney, heart, and the immune system [19-22], is the last straw to kill patients. ERCP-BD is the first choice to relieve the obstructive jaundice caused by HBMO in order to improve quality of life and/or to following chemotherapy/malignancies resection. ERCP-BD for HBMO is performed using the plastic stent (nasobiliary drainage tube) or self-expandable metal stent (SEMS). The purpose of this study was to explore the risk factors for the poor jaundice reducing effect in u-HC patients with HBMO using ERCP-BD. It was identified that u-HC with intra-hepatic metastasis was an only risk factor for poor jaundice reduction effect (HR: 8.125, 95% CI: 1.776-37.172, $p<0.05$). We believed that this may ultimately be related to the insufficient residual effective liver volume and the destruction of liver micro-environment. It was reported that γ-GGT sensitively reflected the extent of malignant obstruction in the low bile duct, and γ-GGT was positively correlated to TB [23]. In this paper, we did not find that there was a significant difference in the value of γ-GGT pre-ERCP between the jaundice-reducing effective group and the jaundice-reducing ineffective group (508.0 *vs.*486.9 U/L), nor the other liver function indexes. We also did not find age, gender, stricture length, gallstones, pre-procedure tumor markers, pre-procedure PT, sphincterotomy status, the highest level of post-procedure amylase and WBC, PTBD before or after ERCP-BD and biliary drainage time were significantly correlated with reducing jaundice effect. We speculated that the load of the malignancy itself was the root cause of elevated liver function indexes or prolonged PT. It was reported that transient bacteremia occurred in approximately 2% of patients after biliary intervention [24]. The attack of cholangitis would seriously lead to early stent occlusion, aggravate the deterioration of liver function and even multiple organ dysfunction, which eventually affected the effect of ERCP-BD. Therefore, all patients scheduled for biliary drainage should receive prophylactic antibiotic prior to the ERCP-BD procedure and if a patient developed cholangitis following biliary intervention, antibiotics should be continued [25]. In our paper, we found that the temperature and the rate of patients with maximum body temperature exceeding 38℃ post ERCP-BD was slightly higher in the jaundice-reducing effective group than in the ineffective group, too (38.1 *vs.* 37.8℃, 0.52 *vs.* 0.31, respectively). High body temperature seemed to be a protective factor. To put it another way, maybe the high temperature after ERCP-BD may prompt clinicians to use antibiotics for a long time, and they would use the methods of blood culture drug sensitivity test to find the appropriate antibiotics. In our study, the jaundice-reducing effective rate in Bismuth type I was 100% (1/1), in Bismuth type II was 83.3% (5/6), in Bismuth type III was 100% (2/2), and in Bismuth IV was 50.0% (15/30). We did not find that the above classification was significantly related to the jaundice reducing effect in patients with HBMO using ERCP-BD. Similarly, it had been reported that the final overall drainage success rates in type I: was 91%, type II was 83% and type III was 73% [26]. In controversy, previous study suggested that ERCP-BD must be avoided in type III stenosis because of the high rate of 30-day mortality [27]. Unfortunately, we had not concluded that bilateral drainage was better than unilateral drainage. This may be related to our definition of "bilateral" and "unilateral". We taken only PTBD drainage or nasobiliary drainage as unilateral drainage because the above drainage was located in the intra-hepatic bile duct, not in the common hepatic duct. There were some limits in our study: first, the number of patients was not large enough; second, it was a retrospective study; third, previous study reported that successful drainage was defined as a decrease in total bilirubin of more than 30% [28]; in our study, successful drainage was defined as a decrease both in TB and DB more than 20%. We had this definition based on the following considerations: we were not considering the effect of reducing jaundice one month after ERCP or at a fixed time. Our observation time was from the day of ERCP operation to the end of patient discharge.

6. Conclusion

In conclusion, ERCP was an effective method to relieve the obstruction in u-HC patients with HBMO. Careful patient selection for treatment was very important, and patients with multiple intra-hepatic metastases should be avoided.

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