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RAPID COMMUNICATION

Risk factors of acute cholecystitis after endoscopic common bile duct stone removal

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Abstract

AIM: To evaluate the risk factors of acute cholecystitis after endoscopic common bile duct (CBD) stone removal.

METHODS: A total 100 of patients who underwent endoscopic CBD stone removal with gallbladder (GB) *in situ* without subsequent cholecystectomy from January 2000 to July 2004 were evaluated retrospectively. The following factors were considered while evaluating risk factors for the development of acute cholecystitis: age, gender, serum bilirubin level, GB wall thickening, cystic duct patency, presence of a GB stone, CBD diameter, residual stone, lithotripsy, juxtapapillary diverticulum, presence of liver cirrhosis or diabetes mellitus, a presenting illness of cholangitis or pancreatitis, and procedure-related complications.

RESULTS: During a mean 18-mo follow-up, 28 (28%) patients developed biliary symptoms; 17 (17%) acute cholecystitis and 13 (13%) CBD stone recurrence. Of patients with acute cholecystitis, 15 (88.2%) received laparoscopic cholecystectomy and 2 (11.8%) open cholecystectomy. All recurrent CBD stones were successfully removed endoscopically. The mean time elapse to acute cholecystitis was 10.2 mo (1-37 mo) and that to recurrent CBD stone was 18.4 mo. Of the 17 patients who received cholecystectomy, 2 (11.8%) developed recurrent CBD stones after cholecystectomy. By multivariate analysis, a serum total bilirubin level of <1.3 mg/dL and a CBD diameter of <11 mm at the time of stone removal were found to predict the development of acute cholecystitis.

CONCLUSION: After CBD stone removal, there is no need for routine prophylactic cholecystectomy. However, patients without a dilated bile duct (<11 mm) and jaundice (<1.3 mg/dL) at the time of CBD stone removal have a higher risk of acute cholecystitis and are possible candidates for prophylactic cholecystectomy.

Key words: Sphincterotomy; Choledocholithiasis; Acute cholecystitis; Cholecystectomy

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INTRODUCTION

Endoscopic sphincterotomy is the treatment of choice for patients with common bile duct (CBD) stones. The high success rate and safety of this modality have been well established by a number of studies[1-5]. Because gallstones may pass from the gallbladder (GB) into the CBD, calculous GB is considered to be one of the risk factors for the recurrence of bile duct stones after sphincterotomy[4,6]. Some studies have compared the results of the wait-and-see policy and prophylactic cholecystectomy to prevent biliary complications but arrived at contradictory results[7-9]. Thus, it still remains controversial as to whether subsequent laparoscopic cholecystectomy is indicated in patients with concurrent GB stones. Most studies have focused on the identification of predictors of CBD stone recurrence, which can be treated again endoscopically without surgery; however, the development of acute cholecystitis is a definite indication of cholecystectomy. So the risk factors of subsequent acute cholecystitis are more important than those of recurrent CBD stones in terms of the decision concerning prophylactic cholecystectomy. However, few studies have identified the risk factors of acute cholecystitis after endoscopic CBD stone removal in patients with GB *in situ*. The aims of this study were to assess the risks of biliary symptom recurrence and to identify the risk factors of acute cholecystitis in patients with GB *in situ* who have received endoscopic CBD stone removal.

MATERIALS AND METHODS

Patients

The medical records of patients with GB *in situ* who

Table 1 Baseline characteristics and CBD stone recurrence

	Cholecystectomy due to acute cholecystitis	
	Yes (n=17)	No (n=83)
Mean age±SD	58.9±16.3	65.4±12.0
Gender (M/F)	8/9	54/29
Recurrence of CBD stone	2/17 (11.8%)	11/83 (13.2%)

underwent endoscopic CBD stone removal for the first time in our hospital from January 2000 to July 2004 were reviewed. Patients were excluded if another neoplasm or acute cholecystitis was diagnosed at the time of CBD stone removal, and if they had undergone prophylactic cholecystectomy after CBD stone removal.

The diagnosis of CBD stone was made by either ultrasonography (USG) or computed tomography (CT) before endoscopic retrograde cholangiopancreatography (ERCP) in the majority of patients, but a definite diagnosis was defined as visible CBD stones on ERCP. The presence of GB stone was evaluated using USG, CT, and ERCP and the wall thickness of GB was evaluated using either USG or CT. Patients with no visible stone on all imaging modalities were allocated to the no GB stone group. The patients who required treatment for a CBD stone 6 mo after complete endoscopic stone removal were defined as having CBD stone recurrence. Radiological data were analyzed using a digitalized picture archiving communication system (PACS). Patient records were checked in each case to ascertain whether cholecystectomy due to acute cholecystitis was done or not after endoscopic CBD stone removal, and telephone calls were made to determine this in the few patients lost during follow-up.

Endoscopy protocol

Duodenal endoscopic intubation (TJF-240, Olympus, Tokyo, Japan) was performed under midazolam sedation. Sphincterotomy was performed in all the patients using a standard sphincterotome and/or a needle knife. After visualizing a CBD stone by cholangiography under fluoroscopic guidance, stones were extracted using a stone basket, balloon catheter, or a mechanical lithotripter according to stone size.

Statistical analysis

Data were analyzed using a statistical software package (SPSS, version 12.0; SPSS Inc.). Differences between the groups were analyzed using the χ^2 test. Logistic regression analysis was used to estimate odds ratios. The cumulative rate of acute cholecystitis requiring cholecystectomy was calculated using the Kaplan-Meier method.

RESULTS

Patient population

During the study, a total of 1 986 patients underwent ERCP at our hospital. The diagnosis of a CBD stone was made for 452 (22.8%) patients, and endoscopic CBD stone removal was performed successfully in 414 (91.6%) patients. Of these, 198 (47.8%) had a GB *in situ* at the time of endoscopic CBD stone removal. Forty-seven (23.7%) patients had a previous history of endoscopic CBD stone removal more than once, and 38 patients (19.1%) received subsequent cholecystectomy for the management of acute cholecystitis. Another 3 (1.5%) patients who experienced incidental cholecystectomy during cancer surgery (2 for gastric cancer and 1 for hepatoma) and 12 (6.0%) patients with inadequate medical information were omitted from the analysis. The total number of study subjects subjected to analysis was 100. No prophylactic cholecystectomy was planned during the follow-up for these patients.

Recurrence of biliary complications after endoscopic CBD stone removal

During a mean 18-mo follow-up, 28 (28%) patients developed biliary symptoms; 17 (17%) with acute cholecystitis and 13 (13%) with CBD stone recurrence. No difference was observed between those who received cholecystectomy and those who did not receive cholecystectomy in terms of mean age or gender (Table 1). The mean time elapsed between original CBD stone removal and acute cholecystitis was 10.2 mo (1-37 mo). Of the 17 patients who received cholecystectomy, 2 patients (11.8%) developed recurrent CBD stones after cholecystectomy. The CBD stone recurrence rate in patients without acute cholecystitis was 13.2% (11/83). All cases of CBD stone recurrence were managed by endoscopic stone removal without surgery. The mean time elapsed (±SD) from endoscopic CBD stone removal to the development of acute cholecystitis was 10.2 (±10.6) mo with a range of 1-37 mo. All the patients in whom acute cholecystitis developed received emergency or elective cholecystectomy. Laparoscopic cholecystectomy was performed for all the patients initially and in 2 of the 17 patients (11.8%) the operation was converted to open cholecystectomy. The mean follow-up time (±SD) of the patients in whom acute cholecystitis did not occur was 18.4 mo (±9.8) and the range was 4-44 mo.

Risk factors for acute cholecystitis after endoscopic CBD stone removal

The results of univariate analysis of potential risk factors for the development of acute cholecystitis after endoscopic CBD stone removal are shown in Table 1. Of the 15 variables, total bilirubin <1.3 mg/dL, the presence of a GB stone and a CBD diameter <11 mm were found to be significant by univariate analysis (P=0.01, 0.02, and 0.03, respectively). However, multiple logistic regression analysis with forward selection and backward elimination identified only total bilirubin <1.3 mg/dL and CBD diameter <11 mm, and both variables reached statistical significance (Tables 2 and 3). Cumulative rates of acute cholecystitis requiring cholecystectomy, according to these two variables were calculated by the Kaplan-Meier method as shown in Figures 1 and 2.

DISCUSSION

The present study found that the overall recurrence rate of CBD stone after endoscopic CBD stone removal was 13%

Table 2 Univariate analysis of potential risk factors for the development of acute cholecystitis after endoscopic CBD stone removal

Variable	*n*	Acute cholecystitis (%)	OR[1]	95%CI[2]	*P* value
Gender					
Male	62	8 (12.9)	1		
Female	38	9 (23.7)	2.10	0.73-6.01	0.13
Age					
⩾60 yr	74	11 (14.9)	1		
<60 yr	26	6 (23.1)	1.72	0.56-5.24	0.25
Total bilirubin					
⩾1.3 mg/dL	67	7 (10.6)	1		
<1.3 mg/dL	33	10 (31.3)	3.83	1.29-11.31	0.01
GB wall thickening					
No	77	13 (16.9)	1		
Yes	23	4 (17.4)	1.04	0.30-3.56	0.59
Patency of cystic duct					
No	45	8 (17.8)	1		
Yes	55	9 (16.4)	0.91	0.32-2.58	0.53
Presence of GB stone					
No	48	4 (8.3)	1		
Yes	52	13 (25.0)	3.67	1.10-12.18	0.02
CBD diameter					
⩾11.5 mm	88	12 (13.6)	1		
<11.5 mm	12	5 (41.7)	4.52	1.23-16.59	0.03
Residual stone					
No	91	15 (16.5)	1		
Yes	9	2 (22.2)	1.45	0.27-7.66	0.48
Lithotripsy					
Yes	13	0 (0)	1		
No	87	17 (19.5)	1.24	1.12-1.38	0.11
Diverticulum					
No	57	11 (19.3)	1		
Yes	43	6 (14.0)	0.68	0.23-2.01	0.34
Liver cirrhosis					
No	92	15 (16.3)	1		
Yes	8	2 (25.0)	1.71	0.32-9.30	0.41
Diabetes mellitus					
No	88	16 (18.2)	1		
Yes	12	1 (8.3)	0.41	0.05-3.40	0.35
Cholangitis at ERCP					
No	71	14 (19.7)	1		
Yes	29	3 (10.3)	0.47	0.12-1.78	0.20
Pancreatitis at ERCP					
No	88	15 (17.1)	1		
Yes	12	2 (16.7)	0.97	0.19-4.90	0.67
Complication after ERCP					
No	95	16 (16.8)	1		
Yes	5	1 (20.0)	1.23	0.13-11.79	0.61

[1]Odds ratio; [2]confidence interval.

Table 3 Multivariate analysis of potential risk factors for the development of acute cholecystitis after endoscopic CBD stone removal

Variable	OR[1]	95%CI[2]	*P* value
Total bilirubin			
<1.3 mg/dL	4.62	1.39-15.33	0.01
⩾1.3 mg/dL	1		
CBD diameter			
<11.5 mm	5.10	1.19-21.80	0.03
⩾11.5 mm	1		
Presence of GB stone			
Yes	2.98	0.83-10.63	0.09
No	1		

[1]Odds ratio; [2]confidence interval.

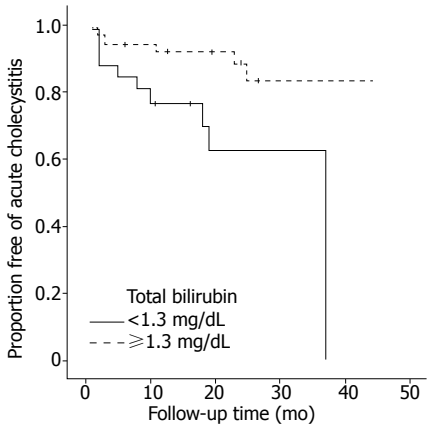

Figure 1 Kaplan–Meier's curve comparing two total bilirubin levels in relation to the development of acute cholecystitis. Patients with a total bilirubin of <1.3 mg/dL developed acute cholecystitis more frequently than patients with a level of ⩾1.3 mg/dL (P=0.01, log-rank test).

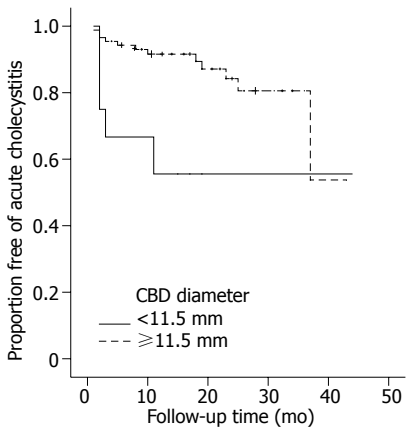

Figure 2 Kaplan–Meier's curve comparing two CBD diameters in relation to acute cholecystitis development. Patients with CBD diameters <11 mm developed acute cholecystitis more frequently than patients with CBD diameters of ⩾11 mm (P=0.03, log-rank test).

(13/100), and that the frequency of acute cholecystitis after endoscopic CBD stone removal was 17% (17/100). Because two patients in whom acute cholecystitis developed also experienced CBD stone recurrence and there was no case of cholangitis or CBD stricture, the overall recurrence rate of biliary-related events during follow-up after endoscopic CBD stone removal was 28% (28/100), which is similar to the rates of 5-24% reported previously[1,2,4,6,8-28].

The advisability of prophylactic cholecystectomy to prevent biliary complications after endoscopic CBD stone removal remains a matter of debate; even

recent prospective[7] and large scale cohort studies[9] produced contrary conclusions concerning prophylactic cholecystectomy *vs* the wait-and-see approach. Moreover, because no consensus has been reached, the decision as to whether to operate or not is made empirically on a case-by-case basis[8,13,17-19]. However, two important points should not be missed. The first is that, as presented by previous studies and ours, the occurrence of acute cholecystitis requiring cholecystectomy is not uncommon and the second is that morbidities such as bile duct injury and mortality caused by laparoscopic cholecystectomy are not negligible[29-31]. Recurrent CBD stones can be retreated endoscopically without surgery but the development of acute cholecystitis is a definite indication for cholecystectomy. Thus the risk factors of subsequent acute cholecystitis are more important than that of recurrent CBD stones with respect to decisions concerning prophylactic cholecystectomy. In the present study, the development of acute cholecystitis (17%) was more common than that of CBD stone (13%) recurrence after CBD stone removal. We believed that if the risk factors of acute cholecystitis in patients who receive an endoscopic CBD stone removal could be identified, we might be able to identify the indicators of prophylactic cholecystectomy, as has been mentioned by earlier investigators[13]. Some studies have compared the results of prophylactic cholecystectomy and non-surgical treatment[7,9,17]. However, as far as we know, few studies have addressed the risk factors of acute cholecystitis after endoscopic CBD stone removal in patients with GB *in situ*, and thus our report might be the first to focus on this subject.

After conducting univariate and multivariate analyses to identify potential risk factors, we concluded that the occurrence of acute cholecystitis after endoscopic CBD stone removal was significantly more frequent in patients with a serum total bilirubin level of <1.3 mg/dL and a CBD diameter of <11 mm at the time of ERCP. Interestingly, a dilated CBD was identified as a risk factor of bile duct stone recurrence after endoscopic papillotomy by previous studies[4,6]. However, our results should be interpreted from a different point of view because the pathogenesis of CBD stone recurrence and the development of acute cholecystitis differ. In East Asia the number of primary CBD stone cases is relatively high compared with the number of secondary CBD stones originating from a GB stone as compared with the situation in the West, although the number of secondary CBD stone cases is increasing over the recent years due to the Westernization of diet[32-34]. In patients with GB or CBD stones, the differentiation of primary and secondary CBD stones is practically impossible because GB stones cannot be sampled for chemical analysis endoscopically, even though they are visualized by ERCP. However, considering the fact that patients with a dilated bile duct tend to form new stones in the bile duct and the cystic duct seldom passes large stones, large CBD stones with a dilated CBD are likely to be primary CBD stones[4,26,35,36]. On the other hand, small CBD stones in association with a non-dilated CBD are more likely to originate from the GB. If cholecystectomy is not performed in such patients, acute cholecystitis development due to cystic duct obstruction by a gallstone is a risk during the process of passage[37,38]. The same assumption can be applied to patients with a low total bilirubin level who were found to develop acute cholecystitis more frequently. Of the 17 patients with cholecystectomy, 2 patients (11.8%) developed recurrent CBD stones after cholecystectomy. Thus cholecystectomy did not reduce CBD stone recurrence in our study, which suggests that most CBD stones may have been secondary rather than primary stones in our patients.

According to our data, 4 of 48 patients who were classified as acalculous at the time of ERCP developed acute cholecystitis during follow-up. A review of our operative records revealed that 2 of 4 patients had calculous cholecystitis and that the remaining 2 had no evidence of a GB stone. However, for the two acalculous cholecystitis patients, the possibility of calculous cholecystitis with a previously passed be excluded, because none of them had the well-known predisposing factors of acalculous cholecystitis, i.e., severe illness or old age[39,40].

In conclusion, the present study shows that a serum bilirubin level of <1.3 mg/dL and a CBD diameter of <11 mm at the time of endoscopic CBD stone removal are risk factors for the development of acute cholecystitis requiring cholecystectomy. Although our results are limited due to the retrospective nature of our study, we suggest that prophylactic cholecystectomy should be reserved for patients who have the risk factors of acute cholecystitis. Prospective randomized studies are needed to more definitively establish the risk factors of acute cholecystitis after endoscopic CBD stone removal.

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