The Efficacy of Early Scheduled Follow-Up Endoscopic Retrograde Cholangiopancreatography after Common Bile Duct Stone Removal

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Background/Aims: To investigate the efficacy of early scheduled follow-up endoscopic retrograde cholangiopancreatography (ERCP) after common bile duct (CBD) stone removal.

Methods: Patients who underwent endoscopic CBD stone removal and who had at least one risk factor for stone recurrence were enrolled. Six months after complete clearance of the CBD, patients underwent follow-up ERCP at an ambulatory care center, irrespective of symptoms. **Results:** The incidence of symptoms and cholangitis at follow-up ERCP was significantly lower in Group A (ERCP at 6 months after stone removal) than that in Group B (ERCP at >6 months) (14.3% vs 71.4%, $p=0.00$; 9.5% vs 33.3%, $p=0.02$, respectively). However, the recurrence rates of CBD stones were not different between Groups A and B (33.3% vs 47.6%). When comparing the subgroups, Group AR (stone recurrence in Group A) displayed significantly fewer symptoms and lesser cholangitis and spent fewer days in the hospital than did Group BR (stone recurrence in Group B) (21.4% vs 70%, $p=0.02$; 14.3% vs 60%, $p=0.02$; 2.43 ± 1.87 vs 6.10 ± 3.35 , $p=0.00$, respectively). **Conclusions:** Our data suggest that, irrespective of symptoms, early scheduled follow-up ERCP for patients who are at a high risk of recurrence is effective and safe. (*Gut Liver* 2011;5:65-69)

Key Words: Risk factor; Recurrence; Common bile duct stone; Endoscopic retrograde cholangiopancreatography; Cholangitis

INTRODUCTION

The recurrence rates of common bile duct (CBD) stones after endoscopic stone removal have been reported to range from 4% to 24%.¹⁻⁶ Many risk factors for the recurrence of CBD stones

such as CBD dilatation, acute CBD angulation, perampullary diverticulum (PAD), a history of cholecystectomy and the number of CBD stones have been reported.⁵⁻¹² The early detection and treatment of recurrent CBD stones may help to avoid more serious complication such as acute suppurative cholangitis. Several studies^{8-10,13} have reported that regular clinical follow-up of patients after CBD stones removal is beneficial and it reduces the morbidity related to stone recurrence. However, early detection of CBD stone is not easy even after physical examinations, biochemical tests and ultrasonography. Furthermore, the majority of patients who are without risk factors for recurrence will have no further recurrence after stone removal. Therefore, if follow-up evaluations are restricted to the patients who are at a high risk for recurrence, then the cost of subsequent examinations may be reduced. In addition, if early scheduled follow-up endoscopic retrograde cholangiopancreatography (ERCP) is more accurate to detect stones and it is safer and feasible for removing the recurrent CBD stone as compared with regular clinical follow-up, then it should be the modality of choice to follow-up the patients who are at a high risk for recurrence. So, we conducted a prospective study on patients who are at a high risk for recurrence to evaluate the efficacy of early scheduled follow-up ERCP after CBD stone removal.

MATERIALS AND METHODS

1. Patients

We enrolled the patients who underwent endoscopic CBD stone removal at our institution between October 2005 and September 2008 and who had at least one risk factor for stone recurrence (maximum CBD diameter >15 mm, CBD angle $\leq 145^\circ$, PAD). After complete clearance of the bile duct stones, the patients with at least one risk factor were recommended to

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undergo follow-up ERCP 6 months later irrespective of their symptoms. The patients who refused to undergo early follow-up ERCP were recommended to have regular clinical follow-ups that included an interview and biochemical tests, including liver function tests (LFTs), every 3 months. If recurrent CBD stones were suspected, then they were readmitted and ERCP was performed. The recurrence of CBD stones was defined as the development of stones no earlier than 6 months after the initial complete removal of CBD stone. Written informed consent for the endoscopic procedures was obtained from all the patients.

2. Methods

ERCP was performed by an experienced endoscopist with using a duodenoscope (model JF-240, or TJF-240; Olympus Co., Tokyo, Japan). Endoscopic sphincterotomy (EST) was carried out by using a standard pull-type, push-type or needle-knife papillotome. The extent of EST was done at the discretion of the endoscopist. Supplementary endoscopic papillary balloon dilatation (EPBD) was done using controlled radial expansion balloon catheters (Boston Scientific, Natick, MA, USA). Disappearance of the waist of the balloon was achieved under repeated dilation with a total duration of 1 minute. The stones were extracted and the bile duct was swept by Dormia baskets, retrieval balloons (maximum balloon diameter: 15 mm; Boston Scientific) or both. If a discrepancy existed between the stone size and the ampullary orifice after EST or EPBD, then the stones were fragmented by mechanical lithotripsy (BML 4Q; Olympus Co.) before extraction. After this, a balloon-occluded cholangiogram was carried out to detect any residual stones or debris. When residual stones or debris were detected, they were completely extracted to make the bile duct a 'clean duct.' A 'clean duct' was defined as no residual stone fragments and debris in the extrahepatic bile duct at the final ERCP session. Nevertheless, if there was the possibility of residual stones or debris, then an endoscopic nasobiliary drainage tube was inserted to drain the debris. Successive ERCP procedures were performed until a 'clean duct' was achieved. During the initial ERCP, the maximum CBD diameter, the CBD angle and the number and size of the stones were measured on the cholangiogram obtained after optimal opacification of the

biliary tree. The maximum CBD diameter over the entire length of the extrahepatic bile duct was measured before stone removal with the patient in the prone position. The maximum CBD diameter was corrected for the magnification with using the known diameter of the duodenoscope as a reference. The CBD angle was measured as the sharpest angle along the CBD from 1 cm below the bifurcation to 1 cm above the papilla. PAD was defined as the presence of a diverticulum within a 2 cm radius from the papilla.

3. Statistical analysis

Continuous values were expressed as mean±standard deviation. The categorical parameters were compared by χ^2 tests or Fisher's exact test, and the continuous variables were compared by Student's t-tests. Differences were considered statistically significant for p value <0.05. The statistical analyses were performed with statistical software (SPSS 11.5 for Windows; SPSS Inc., Chicago, IL, USA). This study was approved by the Institutional Review Board of our institution.

RESULTS

During the study period, 190 consecutive patients underwent ERCP for CBD stones at our hospital. Of these, 104 patients were excluded because they had no risk factors for recurrence (n=41) or they had malignancy related CBD stone (n=37), they had undergone choledochotomy (n=14), they had benign stenosis of the CBD (n=6), they had undergone choledochoduodenostomy (n=3) or they had been transferred to another hospital (n=3). Altogether, 86 patients for whom a 'clean duct' had been achieved were subjected to follow up. The 63 patients who underwent follow-up ERCP are included in the analysis and 23 patients were lost to follow up. Of the sixty three patients who were able to be examined by follow-up ERCP, forty two patients (Group A) underwent ERCP at 6 months after CBD stone removal as initially recommended, but twenty-one patients (Group B) underwent ERCP more than 6 months after the initial CBD stone removal because these patients did not follow the study protocol (Fig. 1). The initial baseline characteristics of the patients

Fig. 1. Flow chart summarizing the study. CBD, common bile duct; ERCP, endoscopic retrograde cholangiopancreatogram.

in Groups A and B were similar (Table 1). Follow-up ERCP was performed at 6.14 ± 0.35 months in Group A, but at 14.1 ± 6.34 months in Group B. The reason why the examination in Group B was delayed was the patients did not follow study protocol because they did not have any symptom before a second attack. Most of the Group B patients revisited clinic due to suffering biliary symptoms such as RUQ pain. As expected, the incidence of symptoms and cholangitis at the time of the follow-up ERCP was significantly lower in Group A than that in Group B (14.3% vs 71.4%, $p=0.00$; 9.5% vs 33.3%, $p=0.02$, respectively). Cholangitis is one of the major complications of CBD stone, and it is associated with morbidity and mortality. However, the recurrence rates of CBD stones were not significantly different between Group A (14 of 42, 33.3%) and Group B (10 of 21, 47.6%).

The decision for performing ERCP for detecting stone was based on the clinical symptoms such as RUQ pain, fever and abnormality of the LFTs. In our high risk group of patients, 51.9% of the symptomatic patients revealed stone. Interestingly, 27.8% of the asymptomatic patients also had stones. The asymptomatic patients showed a shorter hospital stay than did the symptomatic patients (Table 2).

DISCUSSION

EST and EPBD are both well-established therapeutic procedures for the treatment of CBD stones.^{9-12,14-20} However, the recurrence

rate of CBD stones has been in the range of 4-24%.¹⁻⁶ Furthermore, most recurrences occur within the first 2 or 3 years^{6,9-11,13} after stone removal and 39-54% of the patients with recurrent stones are asymptomatic.^{8,10,13}

In the present study, the recurrence rate of CBD stone was 38% (24 of 63 patients), which was higher than that reported in most other studies. The higher recurrence rate may be attributable to the fact that we enrolled the patients who had risk factors for recurrence and who underwent follow-up ERCP. In the same time period, there were no recurrences of CBD stone in the patients who were without risk factors for recurrence (data not shown).

Many studies^{8-10,13} have reported that regular clinical follow-up after CBD stone removal is beneficial and it reduces the morbidity related to CBD stone recurrence. However, this strategy is not optimal. The reasons for this are as follow. First, the recurrence rates are dependent on the degree of risk for stone recurrence.^{5,6,9,10,12,13} The majority of patients who are without risk factors for recurrence will have no further recurrence after stone removal. Second, about half of the recurrent CBD stones are asymptomatic.^{8,10,13} Third, the sensitivity of elevated LFTs to detect recurrent CBD stone is low.^{11-13,21} Finally, computed tomography and magnetic resonance cholangiopancreatography are less sensitive to detect small stones in a dilated bile duct and ultimately they are dependent on ERCP for stone removal.^{5,10,13,22,23} In addition, follow-up ERCP has been proven to be safer^{11,13,14,24,25} than the initial ERCP. Therefore, the ideal follow-up strategy after CBD stone removal is to follow up the high risk patients with ERCP. This strategy will detect recurrent CBD stone early and decrease the incidence of more serious complications such as acute suppurative cholangitis, which has high mortality if it is not treated. Our results mean that the target of the follow-up strategy is the patients who are at a high risk for recurrence.

Table 1. Baseline Characteristics of Groups A and B at the Time of the Initial ERCP

	Group A (n=42)	Group B (n=21)	p-value
Age, mean $\pm$ SD, yr	65.52 $\pm$ 11.84	69.52 $\pm$ 11.04	NS
Gender, female, %	73.8	66.7	NS
CBD stone removal Hx, %	23.8	23.8	NS
LC Hx/GB stone, %	35.7/26.2	33.3/23.8	NS
LFT	-*	-*	NS
PAD, %	47.6	66.7	NS
Stone size, mean $\pm$ SD, mm	12.97 $\pm$ 5.18	13.39 $\pm$ 7.08	NS
Stone no. (≥ 2), %	47.6	66.7	NS
CBD diameter, mean $\pm$ SD, mm	20.03 $\pm$ 7.14	20.12 $\pm$ 4.55	NS
CBD angulation, mean $\pm$ SD, °	131.16 $\pm$ 13.52	124.24 $\pm$ 20.17	NS
IHD stone/stricture, %	7.1/2.4	23.8/14.3	NS
EST (medium/maximum), %	81/19	81/19	NS
EPBD/ENBD/ML, %	45.2/52.4/9.5	47.6/52.4/28.6	NS

ERCP, endoscopic retrograde cholangiopancreatography; SD, standard deviation; NS, not significant; CBD, common bile duct; Hx, history; LC, laparoscopic cholecystectomy; GB, gallbladder; LFT, liver function test; PAD, perampullary diverticulum; IHD, intrahepatic duct; EST, endoscopic sphincterotomy; EPBD, endoscopic papillary balloon dilatation; ENBD, endoscopic nasobiliary drainage; ML, mechanical lithotripsy.

*The LFT between the groups were not significantly different.

Table 2. Clinical Characteristics of the Asymptomatic and Symptomatic Groups at the Time of Follow-Up ERCP

	Sx (-) (n=36)	Sx (+) (n=27)	p-value
Term between ERCP, m	6.92 $\pm$ 2.53	11.30 $\pm$ 6.72	0.00
Recurrence rate, %	27.8	51.9	NS
Stone no. (≥ 2), %	20.0	36.4	NS
Stone size, mean $\pm$ SD, mm	4.61 $\pm$ 7.86	8.53 $\pm$ 7.59	NS
EPBD, %	5.6	25.9	0.02
ENBD, %	2.8	14.8	NS
Mechanical lithotripsy, %	0.0	0.0	NS
Complication, %	0.0	7.4	NS
ERCP session no. (≥ 2), %	5.6	14.8	NS
Hospital days, mean $\pm$ SD, day	1.22 $\pm$ 0.80	4.07 $\pm$ 3.05	0.00

ERCP, endoscopic retrograde cholangiopancreatography; Sx, symptom; NS, not significant; SD, standard deviation; EPBD, endoscopic papillary balloon dilatation; ENBD, endoscopic nasobiliary drainage.

Table 3. Clinical Characteristics and Recurrence Rates of Groups A and B at the Time of Follow-Up ERCP

	Group A (n=42)	Group B (n=21)	p- value
Time period between ERCP procedures, mo	6.14±0.35	14.1±6.34	0.00
Symptoms, %	14.3	71.4	0.00
Cholangitis, %	9.5	33.3	0.02
LFT	—*	—*	NS
F/U duration, mean±SD, mo	24.55±13.53	37.38±15.37	0.00
Recurrence rate, n (%)	14 (33.3)	10 (47.6)	NS

ERCP, endoscopic retrograde cholangiopancreatography; LFT, liver function test; NS, not significant; F/U, follow up; SD, standard deviation.

*The LFTs between the groups were not significantly different.

Irrespective of the statistically similar recurrence rates, the early scheduled follow-up ERCP group (Group A) had a significantly lower frequency of symptoms and cholangitis than that of the late symptom based follow-up ERCP group (Group B) (Table 3). Bile duct stone, once biliary type pain and cholangitis developed, was associated with a prolonged hospital stay. The stone recurred patients in the early scheduled follow-up ERCP group (Group AR) revealed a lesser frequency of symptoms and cholangitis and a smaller size of stone. Consequently, a shorter hospital stay was achieved in early scheduled follow-up ERCP group (Table 4).

In terms of symptoms, the recurrence rates between the asymptomatic and symptomatic groups were not significantly different, but the recurrence rate tended to be higher in the symptomatic patients than that in the asymptomatic patients. Still, 27.8% of the asymptomatic patients revealed stone on the follow-up ERCP. These results indicate the presence of symptoms is not a good parameter for predicting stone recurrence. The hospital stay of the asymptomatic patients (1.22 days) was shorter than that of the symptomatic patients (4.07 days). At least 22% (14 out of 63 patients) of the patients in the high risk group had recurred stone within 6 months regardless of symptoms. These results indicate that stones recur earlier than previously reported in the high risk group, and the results also indicate that performing early scheduled follow-up ERCP in the high risk patients is reasonable. Recurred stones exist asymptotically for a period of time, but they may cause symptoms or cholangitis at some time in their natural course. Asymptomatic stones are more feasible to safely remove than symptomatic stones. So, we performed follow-up ERCP at the ambulatory care center. No post ERCP complications were observed in Group A. The LFTs of Group A and Group B at the time of follow-up ERCP were not significantly different. This means that the sensitivity of LFTs to detect recurrent CBD stone is low.^{11-13,21} Geenen *et al.*²⁴ reported that for patients with frequent CBD stone recurrences and who were without any obvious predisposing factors, annual

Table 4. Comparison of Clinical Characteristics between Groups AR and BR at the Time of Follow-Up ERCP

	Group AR (n=14)	Group BR (n=10)	p- value
Time period between ERCP procedures, mo	6.07±0.27	15.8±7.89	0.00
Symptoms, %	21.4	70.0	0.02
Cholangitis, %	14.3	60.0	0.02
Stone no. (≥2), %	21.4	30.0	NS
Stone size, mean±SD, mm	5.41±7.90	8.68±7.65	NS
EPBD, %	35.7	40.0	NS
ENBD, %	14.3	30.0	NS
Mechanical lithotripsy, %	0.0	0.0	NS
Complications, %	0.0	10.0	NS
ERCP session no. (≥2), %	21.4	30.0	NS
Hospital days, mean±SD, day	2.43±1.87	6.10±3.35	0.00

ERCP, endoscopic retrograde cholangiopancreatography; SD, standard deviation; EPBD, endoscopic papillary balloon dilatation; ENBD, endoscopic nasobiliary drainage; NS, not significant.

ERCP surveillance, and even if the patients were asymptomatic, decreased the incidence of recurrent episodes of ascending cholangitis as well as its associated morbidity and mortality. This decrease in the incidence of cholangitis was noted despite that there was apparent evidence of recurrent CBD stones in 80% of the patients. In the present study, considering the high recurrence rates of CBD stones in the high risk patients, our results are promising that early scheduled follow-up ERCP with stone removal and clearing of sludge in the bile duct reduced the rate of serious complications. Additionally, although we did not analyze the cost-effectiveness of early scheduled follow-up ERCP, this strategy may be cost-effective owing to the reduced rate of serious complication and short hospital stay. To summarize: we recommend early scheduled follow-up ERCP for the patients who are at a high risk of recurrence, irrespective of symptoms. However, this study is a single center, non-randomized study, so a multicenter randomized prospective study is needed to more accurately define the benefits and proper timing of early scheduled follow-up ERCP.

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The authors have no conflict of interest to declare.

REFERENCES

- Hammarström LE, Stridbeck H, Ihse I, et al. Long-term follow-up after endoscopic treatment of bile duct calculi in cholecystectomized patients. *World J Surg* 1996;20:272-276.
- Bergman JJ, van der Mey S, Rauws EA, et al. Long-term follow-up after endoscopic sphincterotomy for bile duct stones in patients

- younger than 60 years of age. *Gastrointest Endosc* 1996;44:643-649.
3. Sugiyama M, Atomi Y. Follow-up of more than 10 years after endoscopic sphincterotomy for choledocholithiasis in young patients. *Br J Surg* 1998;85:917-921.
 4. Prat F, Malak NA, Pelletier G, et al. Biliary symptoms and complications more than 8 years after endoscopic sphincterotomy for choledocholithiasis. *Gastroenterology* 1996;110:894-899.
 5. Sugiyama M, Atomi Y. Risk factors predictive of late complications after endoscopic sphincterotomy for bile duct stones: long-term (more than 10 years) follow-up study. *Am J Gastroenterol* 2002;97:2763-2767.
 6. Keizman D, Ish Shalom M, Konikoff FM. Recurrent symptomatic common bile duct stones after endoscopic stone extraction in elderly patients. *Gastrointest Endosc* 2006;64:60-65.
 7. Keizman D, Shalom MI, Konikoff FM. An angulated common bile duct predisposes to recurrent symptomatic bile duct stones after endoscopic stone extraction. *Surg Endosc* 2006;20:1594-1599.
 8. Ueno N, Ozawa Y, Aizawa T. Prognostic factors for recurrence of bile duct stones after endoscopic treatment by sphincter dilation. *Gastrointest Endosc* 2003;58:336-340.
 9. Ohashi A, Tamada K, Wada S, et al. Risk factors for recurrent bile duct stones after endoscopic papillary balloon dilation: long-term follow-up study. *Dig Endosc* 2009;21:73-77.
 10. Cheon YK, Lehman GA. Identification of risk factors for stone recurrence after endoscopic treatment of bile duct stones. *Eur J Gastroenterol Hepatol* 2006;18:461-464.
 11. Costamagna G, Tringali A, Shah SK, Mutignani M, Zuccalà G, Perri V. Long-term follow-up of patients after endoscopic sphincterotomy for choledocholithiasis, and risk factors for recurrence. *Endoscopy* 2002;34:273-279.
 12. Kim DI, Kim MH, Lee SK, et al. Risk factors for recurrence of primary bile duct stones after endoscopic biliary sphincterotomy. *Gastrointest Endosc* 2001;54:42-48.
 13. Lai KH, Lo GH, Lin CK, et al. Do patients with recurrent choledocholithiasis after endoscopic sphincterotomy benefit from regular follow-up? *Gastrointest Endosc* 2002;55:523-526.
 14. Kohn GP, Hassen AS, Banting SW, Mackay S, Cade RJ. Endoscopic management of recurrent primary bile duct stones. *ANZ J Surg* 2008;78:579-582.
 15. Bergman JJ, Rauws EA, Fockens P, et al. Randomised trial of endoscopic balloon dilation versus endoscopic sphincterotomy for removal of bile duct stones. *Lancet* 1997;349:1124-1129.
 16. Ochi Y, Mukawa K, Kiyosawa K, Akamatsu T. Comparing the treatment outcomes of endoscopic papillary dilation and endoscopic sphincterotomy for removal of bile duct stones. *J Gastroenterol Hepatol* 1999;14:90-96.
 17. Arnold JC, Benz C, Martin WR, Adamek HE, Riemann JF. Endoscopic papillary balloon dilation vs. sphincterotomy for removal of common bile duct stones: a prospective randomized pilot study. *Endoscopy* 2001;33:563-567.
 18. Fujita N, Maguchi H, Komatsu Y, et al. Endoscopic sphincterotomy and endoscopic papillary balloon dilatation for bile duct stones: a prospective randomized controlled multicenter trial. *Gastrointest Endosc* 2003;57:151-155.
 19. Disario JA, Freeman ML, Bjorkman DJ, et al. Endoscopic balloon dilation compared with sphincterotomy for extraction of bile duct stones. *Gastroenterology* 2004;127:1291-1299.
 20. Tanaka S, Sawayama T, Yoshioka T. Endoscopic papillary balloon dilation and endoscopic sphincterotomy for bile duct stones: long-term outcomes in a prospective randomized controlled trial. *Gastrointest Endosc* 2004;59:614-618.
 21. Barkun AN, Barkun JS, Fried GM, et al. Useful predictors of bile duct stones in patients undergoing laparoscopic cholecystectomy. *McGill Gallstone Treatment Group. Ann Surg* 1994;220:32-39.
 22. Irie H, Honda H, Kuroiwa T, et al. Pitfalls in MR cholangiopancreatographic interpretation. *Radiographics* 2001;21:23-37.
 23. Mehta SN, Reinhold C, Barkun AN. Magnetic resonance cholangiopancreatography. *Gastrointest Endosc Clin N Am* 1997;7:247-270.
 24. Geenen DJ, Geenen JE, Jafri FM, et al. The role of surveillance endoscopic retrograde cholangiopancreatography in preventing episodic cholangitis in patients with recurrent common bile duct stones. *Endoscopy* 1998;30:18-20.
 25. Sugiyama M, Suzuki Y, Abe N, Masaki T, Mori T, Atomi Y. Endoscopic retreatment of recurrent choledocholithiasis after sphincterotomy. *Gut* 2004;53:1856-1859.