Efficacy and Safety of Endoscopic Removal for Asymptomatic Common Bile Duct Stones in Comparison with Symptomatic Stones

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Objective: Endoscopic removal is recommended for common bile duct stones (CBDs). However, in patients with asymptomatic CBDs, follow-up without treatment may be recommended because of the increased complication risks associated with asymptomatic CBDs removal. The objective of our study was to investigate the efficacy and safety of CBDs removal in asymptomatic patients.
Methods: Consecutive patients with naive papilla who underwent endoscopic retrograde cholangiopancreatography (ERCP) for the treatment of CBDs from April 2016 to August 2020 were retrospectively analyzed. We compared the efficacy and safety of CBDs removal in asymptomatic and symptomatic patients.
Results: We enrolled 300 patients, 53 asymptomatic and 247 symptomatic patients. Endoscopic CBDs removal was successful in all patients, except one symptomatic patient. However, the complete stone removal rate in a single session was significantly higher in the asymptomatic group than that in the symptomatic group. ERCP-related complications did not differ between the asymptomatic and symptomatic patients. The incidence of post-ERCP pancreatitis was similar and liver cirrhosis was the only significant risk factor for pancreatitis.
Conclusion: Complication risks associated with endoscopic CBDs removal was not significantly different between asymptomatic and symptomatic patients. Liver cirrhosis was a significant risk factor of ERCP-related pancreatitis.

Key words: asymptomatic common bile duct stones, ERCP-related complications, ERCP-related pancreatitis

INTRODUCTION

Endoscopic retrograde cholangiopancreatography (ERCP) is recommended for removal of common bile duct stones (CBDs). However, ERCP is associated with a high incidence of procedure-related complications that can be fatal. Post-ERCP pancreatitis (PEP) is the most important complication, with an incidence rate of 3–5% [1] The Guidelines for the Treatment of Cholelithiasis 2016 [2] recommend endoscopic CBDs removal in asymptomatic patients. However, several studies revealed an increased risk of PEP associated with the removal of asymptomatic CBDs with incidence rates of 12.5–21% [3–7] compared with symptomatic CBDs removal (2.2–3.9%). The reason why the PEP risk in the treatment for asymptomatic CBDs is higher than that for symptomatic CBDs remains unknown, and further investigation is obviously needed. In addition, symptomatic CBDs spontaneously disappeared in 19–21% of patients [3–7]. Therefore, follow-up without treatment may be an option for patients with asymptomatic CBDs [7] but it remains unclear whether asymptomatic CBDs should be immediately removed by ERCP.

We performed endoscopic removal in patients with CBDs whose condition allowed, regardless of whether they were symptomatic or asymptomatic. To investigate the efficacy and safety of CBDs removal in patients with asymptomatic CBDs, we compared the outcomes and complications of ERCP between asymptomatic and symptomatic CBDs.

PATIENTS AND METHODS

Patients

Patients who underwent endoscopic CBDs removal between April 2016 and August 2020 at Tokai University Hospital were enrolled in this study. We excluded patients who had undergone endoscopic sphincterotomy (EST), endoscopic papillary balloon dilation (EPBD), Billroth II or Roux-en-Y reconstruction before the present study, as well as those with biliary pancreatitis. Patients were divided into asymptomatic and symptomatic groups, and the efficacy and safety of endoscopic CBDs removal were compared. This study was approved by the Institutional Ethics Review Board of Tokai University Hospital (20R-028) and informed consent was obtained from all patients. The investigation conforms with the principles outlined in the Declaration of Helsinki.

Endoscopic Procedures

Side-viewing duodenoscopes (JF-260V or TJF-260V; Olympus, Tokyo, Japan) were used in all patients. We intravenously administered midazolam and pethidine

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hydrochloride as sedatives, scopolamine butylbromide or glucagon to reduce spasms in the gastrointestinal tract, and protease inhibitors and antibiotics to prevent PEP. Diclofenac suppositories were administered to the patients who underwent ERCP in May 2019.

We attempted a contrast-assisted cannulation to access the biliary tract. Needle-knife fistulotomy (NKF) was performed when biliary cannulation using a conventional technique failed. We performed EST or EPBD to allow CBDs extraction through the ampulla of Vater. EPBD was chosen for patients taking anticoagulants or those with large CBDs. We used basket or balloon catheters to extract stones and performed extracorporeal shock wave lithotripsy (ESWL) in cases where endoscopic CBDs removal failed. Endoscopic retrograde biliary drainage (ERBD) or endoscopic nasobiliary drainage (ENBD) was performed to prevent cholangitis if the stones were not completely removed at the end of the procedure. To prevent PEP, endoscopic retrograde pancreatic drainage (ERPD) was performed at the endoscopist's discretion. An endoscopist was categorized as a trainee if he/she had been involved in the ERCP procedure for ≤ 4 years.

Definitions

Asymptomatic CBDs were defined as stones that did not manifest any symptoms, including biliary colic pain or abnormal blood chemistry. The diagnosis of CBDs was made using imaging modalities including abdominal ultrasonography, computed tomography (CT), and magnetic resonance cholangiopancreatography (MRCP). A large stone was defined as a stone with a diameter ≥ 10 mm, and the CBDs diameter represented the diameter of the largest stone if multiple stones were present. Dilatation of the common bile duct was defined as a common bile duct diameter ≥ 10 mm.

Complications of ERCP were defined as any adverse events occurring after endoscopy that required an extension of hospital stay, based on the consensus criteria by Cotton *et al.* [8] We diagnosed PEP when patients complained of merging or worsened abdominal pain with ≥ 3-fold elevation of serum amylase levels above the upper limit of normal. Elevation of serum amylase by ≥ 3-fold the upper limit without accompanying abdominal pain was categorized as post-ERCP hyperamylasemia. Cholangitis was diagnosed according to the Tokyo Guidelines for Management of Acute Cholangitis and cholecystitis published in 2018 (TG2018) [9].

Statistical Analyses

We compared the demographic data, CBDs characteristics, outcome of endoscopic stone removal, and procedure-related complications between the asymptomatic and symptomatic groups. Statistical differences in categorical and numerical variables were analyzed using Fisher's exact and Student's t-tests, respectively. Multivariate analysis was performed using a multiple logistic regression model, which included risk factors ($P < 0.3$ in the univariate analysis. All statistical analyses were performed using SPSS version 26 (IBM Corp., Armonk, NY, USA). Statistical significance was set at $P < 0.05$.

RESULTS

Patient Characteristics (Table 1)

We enrolled 300 consecutive patients including 53 asymptomatic and 247 symptomatic patients (Figure). The mean ± standard deviation (SD) age of the asymptomatic and symptomatic group was 70.2 ± 11.2 and 73.8 ± 12.5 years, respectively ($P = 0.46$). Sex, body mass index (BMI) and underlying diseases did not differ significantly between the two groups but the serum levels of aspartate aminotransferase (AST), alanine aminotransferase (ALT), gamma-glutamyl transpeptidase (γ-GPT), total bilirubin, and C-reactive protein (CRP) were significantly higher in the symptomatic group than in the asymptomatic group ($P < 0.001$).

Characteristics of CBDs (Table 2)

There were significantly more patients with dilated common bile ducts and large stones in the symptomatic group than in the asymptomatic group ($P = 0.007$ and $p = 0.01$, respectively). Patients in both groups predominantly had a single stone (64% vs. 53%, $P = 0.13$) while the proportion of patients with black-pigmented stones in the asymptomatic group (64%) was significantly higher than that in the symptomatic group (36%, $P < 0.001$).

Outcome of endoscopic removal of CBDs (Table 3)

Endoscopic CBDs removal was successfully performed in all patients except one symptomatic patient, and the success rate was similar between the two groups. However, the complete stone removal rate in a single session was significantly higher in the asymptomatic group than that in the symptomatic group (89% vs. 70%, $P = 0.006$). The mean ± SD number of ERCP sessions required to completely remove CBDs was 1.4 ± 0.7 in the asymptomatic group, which was significantly lower than that in the asymptomatic group (1.7 ± 1.1, $P = 0.042$). Deep cannulation was unsuccessful in 6 (2%) symptomatic patients and asymptomatic patients were less likely to have a periampullary diverticulum (PAD) than symptomatic patients (19% vs. 42%, $P = 0.002$). Unintentional cannulation of the pancreatic duct was similarly observed in both groups (70% vs. 57%, $P = 0.08$).

EST was performed more frequently in the asymptomatic group than in the symptomatic group (96% vs. 79%, $P = 0.003$), whereas EPBD was performed at the same frequency (11% vs. 11%, $P = 0.93$). Asymptomatic patients underwent ERBD placement after endoscopic CBDs removal less frequently than asymptomatic patients (6% vs. 26%, $P = 0.001$). The frequencies of ENBD and ERPD placement were similar in both groups. Procedure time was not significantly different between the two groups (29.4 ± 14.4 vs 27.1 ± 14.4 min, $P = 0.34$).

Procedure-related complications (Table 4)

Complications were observed in 7.5% and 8.5% of patients in the asymptomatic and symptomatic groups, respectively ($P = 0.82$). Elevation of serum amylase was observed in 17.0% and 7.7% of the asymptomatic and symptomatic groups, respectively, with statistical significance ($P = 0.035$). However, PEP was observed in 3.8% and 2.0% of the asymptomatic and symptomatic

Table 1 Characteristics of patients who underwent endoscopic CBDs removal

Characteristics	Asymptomatic group (n = 53)	Symptomatic group (n = 247)	p value
Age, years	70.2 ± 11.2	73.8 ± 12.5	0.46
Gender, female/male	35/18 (66/34)	151/96 (61/39)	0.51
BMI, kg/m^2	22.0 ± 4.4	22.4 ± 3.8	0.31
Underlying diseases			
Hypertension	23 (43)	131 (53)	0.20
Diabetes mellitus	13 (25)	53 (21)	0.62
Ischemic heart disease	3 (6)	35 (14)	0.09
Cerebrovascular disease	4 (8)	41 (17)	0.09
Chronic kidney disease	20 (38)	63 (26)	0.07
Liver cirrhosis	5 (9)	12 (5)	0.19
Post-cholecystectomy	5 (9)	16 (6)	0.44
Gallbladder stone	37 (70)	180 (73)	0.65
Use of anticoagulants	10 (19)	74 (30)	0.10
ASA-PS score[a], 1/2/3	11/35/7 (21/66/13)	31/162/54 (13/66/22)	0.16
Laboratory findings			
Hemoglobin, g/dL	13.0 ± 2.1	12.1 ± 2.2	0.72
AST, IU/L	23.8 ± 9.5	173.2 ± 260.1	<0.001
ALT, IU/L	21.9 ± 16.7	160.7 ± 190.7	<0.001
γ-GTP, IU/L	56.5 ± 68.3	332.8 ± 303.0	<0.001
Total bilirubin, mg/dL	0.9 ± 0.4	2.3 ± 2.2	<0.001
CRP, mg/L	1.5 ± 5.4	5.8 ± 7.5	<0.001

Data are presented as n (%) or mean ± standard deviation.
[a]ASA-PS (American Society of Anesthesiologists Physical Status Classfication) score is defined as (1) A normal healthy patient; (2) A patient with mild systemic disease; (3) A patient with severe systemic disease; (4) A patient with severe systemic disease that is a constant threat to life; (5) A moribund patient who is not expected to survive without the operation; (6) A declared brain-dead patient whose organs are being removed for donor purposes.

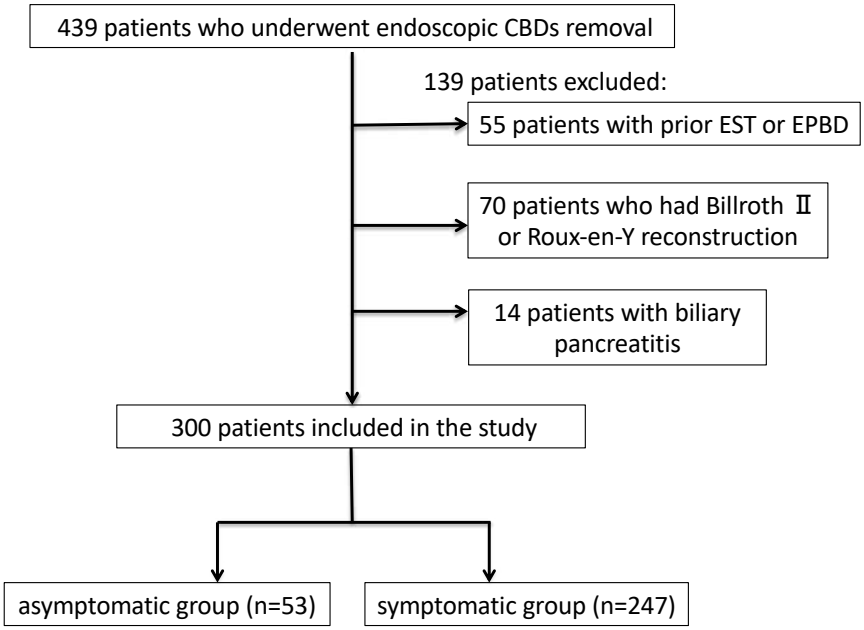

Figure Flow chart of patients who underwent endoscopic CBDs removal

groups, respectively, without statistical significance (P = 0.44). One symptomatic patient progressed to moderate pancreatitis; however, in most cases (two asymptomatic and four symptomatic patients), pancreatitis was mild. Cholangitis occurred in 2 (3.8%) patients in the asymptomatic group and in 12 (4.9%) patients in the symptomatic group (P = 0.73). Bleeding and aspiration pneumonia were noted in 2 (0.8%) symptomatic patients. No procedure-related perforations or deaths occurred.

Risk Factors for PEP (Table 5)

We analyzed the risk factors associated with PEP. In univariate analysis, liver cirrhosis was identified as

Table 2 Characteristics of CBDs

	Asymptomatic group (n = 53)	Symptomatic group (n = 247)	p value
Dilated common bile duct, n (%)	19 (36)	139 (56)	0.007
Large stone, n (%)	7 (13)	76 (31)	0.01
Single stone, n (%)	34 (64)	130 (53)	0.13
Black pigmented stone, n (%)	34 (64)	89 (36)	<0.001

Table 3 The details of endoscopic procedures for CBDs removal

	Asymptomatic group (n = 53)	Symptomatic group (n = 247)	p value
Use of diclofenac suppositories	10 (19)	31 (13)	0.22
Trainee endoscopists	31 (58)	134 (54)	0.57
Presence of PAD	10 (19)	103 (42)	0.002
Pancreatic cannulation	37 (70)	140 (57)	0.08
PGW-assisted cannulation	12 (23)	48 (19)	0.60
Precut sphincterotomy	2 (4)	7 (3)	0.72
Unsuccessful cannulation	0 (0)	6 (2)	0.25
EST	51 (96)	194 (79)	0.003
EPBD	6 (11)	27 (11)	0.93
ERBD	3 (6)	64 (26)	0.001
ENBD	2 (4)	5 (2)	0.44
ERPD	3 (6)	16 (6)	0.83
Procedure time, min	29.4 ± 14.4	27.1 ± 14.4	0.34
Procedure time > 30min	19 (36)	86 (35)	0.89
Complete stone removal	53 (100)	246 (100)	0.64
Complete stone removal in a single session	47 (89)	174 (70)	0.006
Number of ERCP, sessions	1.4 ± 0.7	1.7 ± 1.1	0.042

Data are presented as n (%) or mean ± standard deviation.
PAD Periampullary diverticulum; PGW Pancreatic guide wire; EST Endoscopic sphincterotomy; EPBD Endoscopic papillary balloon dilatation; ERBD Endoscopic retrograde biliary drainage; ENBD Endoscopic nasobiliary drainage; ERPD Endoscopic retrograde pancreatic drainage; ERCP Endoscopic retrograde cholangiopancreatography

Table 4 Procedure-related complications

	Asymptomatic group (n = 53)	Symptomatic group (n = 247)	p value
All, n (%)	4 (7.5)	21 (8.5)	0.82
Pancreatitis, n (%)	2 (3.8)	5 (2.0)	0.44
Mild/moderate/severe	2/0/0	4/1/0	
Hyperamylasemia, n (%)	9 (17.0)	19 (7.7)	0.035
Bleeding, n (%)	0 (0)	2 (0.8)	0.51
Cholangitis, n (%)	2 (3.8)	12 (4.9)	0.73
Aspiration pneumonia, n (%)	0 (0)	2 (0.8)	0.51

a risk factor for PEP development (P = 0.008). Liver cirrhosis was the only significant risk factor in the multivariate analysis (odds ratio [OR], 10.963; 95% confidence interval [CI], 1.712–70.212; P = 0.011). Both patients who progressed to PEP were diagnosed as Child-Pugh A liver cirrhosis. The number of cirrhotic patients who developed PEP was so small that we could not perform further investigation. PEP occurred in 4 (1.6%) of 245 patients who underwent EST and in 3 (5.5%) of 55 patients who did not undergo EST. EST performance tended to reduce PEP, although the difference was not statistically significant.

DISCUSSION

The complete stone removal rate in the asymptomatic group was comparable to that in the symptomatic group. However, the complete stone removal rate in a single session tended to be lower in the symptomatic group than in the asymptomatic group, which might be due to poorer medical condition, such as acute cholangitis encountered in the symptomatic group. EST was performed more often in the asymptomatic group, whereas ERBD was performed more often in the symptomatic group.

In our study, common bile duct dilatation was observed more frequently in the symptomatic group than in the asymptomatic group, which could be a

Table 5 Risk factors for PEP

	With PEP (n = 7)	Without PEP (n = 293)	p value Univariate Analysis	Multivariate Analysis	Odds Ratio (95%CI)
Liver cirrhosis, n (%)	2 (29)	15 (5)	0.008	0.011	10.963 (1.712–70.212)
EST not performed, n (%)	3 (43)	52 (18)	0.09	0.058	NA
PGW-assisted cannulation, n (%)	3 (43)	57 (19)	0.13	0.164	NA
Multiple stones, n (%)	5 (71)	131 (45)	0.16	0.113	NA
Ischemic heart disease, n (%)	2 (29)	36 (12)	0.20	0.193	NA
No use of diclofenac suppositories, n (%)	7 (100)	252 (86)	0.29	0.998	NA
Absence of ERPD, n (%)	6 (86)	275 (94)	0.38		
Large stones (>10 mm), n (%)	1 (14)	82 (28)	0.42		
Trainee endoscopist, n (%)	3 (43)	163 (56)	0.43		
Asymptomatic CBDs, n (%)	2 (29)	51 (17)	0.44		
Pancreatic cannulation, n (%)	5 (71)	172 (59)	0.50		
Non-dilated common bile duct, n (%)	4 (57)	138 (47)	0.60		
Precut sphincterotomy, n (%)	0 (0)	9 (3)	0.64		
Procedure time > 30 min, n (%)	3 (43)	102 (35)	0.66		
Gender (female), n (%)	3 (43)	111 (38)	0.72		
EPBD, n (%)	1 (14)	32 (11)	0.78		
Normal serum bilirubin, n (%)	3 (43)	137 (47)	0.84		
Elderly patients (>75 years), n (%)	4 (57)	159 (54)	0.88		

CI Confidence interval; NA Not applicable

consequence of cholangitis in symptomatic patients. The proportion of black-pigmented stones in the asymptomatic group (64%) was significantly higher than that in the symptomatic group (36%). Such stones, generally formed in the gallbladder, are less likely to cause biliary infections [2]. The rate of black-pigmented stones was comparable to that reported in other studies [3].

In this study, no significant differences were observed in the incidence of complications related to ERCP, including PEP, bleeding, cholangitis, and aspiration pneumonia between the asymptomatic and symptomatic groups. The incidence of PEP was 3.8% in the asymptomatic group, which was not significantly different from that in the symptomatic group (2.0%). According to previous studies, PEP incidence was significantly different: 12.5–21% in the asymptomatic group vs. 2.2–3.9% in the symptomatic group [3–7]. The reason why the PEP incidence in our study was lower than that reported is unclear. Differences in patient background, devices for endoscopic removal, or simultaneously performed procedures might be contributing factors. Female sex, biliary stent placement, non-prophylactic pancreatic duct stent, pancreatic cannulation, and no use of diclofenac suppositories have been suggested [1, 10–14]. We did not find any differences in these risk factors between the asymptomatic and symptomatic groups. Liver cirrhosis was the only factor associated with PEP. According to a recent meta-analysis of six studies, the presence of liver cirrhosis increased the risk of PEP (OR: 1.33, 95%CI: 1.04–1.70) and procedure-related hemorrhage (OR: 2.05, 95%CI: 1.62–2.58) [15]. Although the reason why PEP progresses more frequently in cirrhotic patients is unclear, cirrhosis-related complications, such as poor synthetic function, portal hypertension, or bleeding tendency, might be involved. PAD is known to increase the risk of overall post-ERCP complications [16] and, in our study, PAD was more frequent in the symptomatic group than in the asymptomatic group (42% vs. 19%, P = 0.002). Symptomatic cholangitis may be caused by reflux of intestinal juices accumulated in the PAD into the bile ducts.

However, the natural history of asymptomatic CBDs remains unclear. Spontaneous passage of CBDs through the major papilla occurs in approximately 20–30% of cases within 4–6 weeks after diagnosis [16, 17]. Conversely, another study revealed that a quarter of asymptomatic patients who did not undergo treatment for CBDs experienced CBD-related events [18–20]. Furthermore, the chance of spontaneous passage was as low as 4% for stones larger than 8 mm [21].

PEP can be fatal and although the PEP incidence rate was not higher in asymptomatic than in symptomatic patients in our study, the decision to perform endoscopic CBDs removal in asymptomatic patients should be considered carefully. Follow-up observation may be chosen for elderly patients, those with poor performance status, or serious coexisting illnesses, such as liver cirrhosis. On the other hand, we propose that large stones (≥ 10 mm) found in patients without serious comorbidities should be removed because they have little chance of spontaneous passage.

This study has several limitations. This study was performed retrospectively at a single institution with a relatively small sample size. Therefore, selection bias was unavoidable. The incidence of PEP was 3.8% and 2.0% in asymptomatic and symptomatic patients, re-

spectively. Increasing the number of patients sampled may make a significant difference, especially in the incidence of PEP, but these number appear to be sufficiently low that they would not be affected.

In conclusion, we demonstrated that the risk of endoscopic CBDs removal is not significantly different between asymptomatic and symptomatic patients. Asymptomatic CBDs may be treated safely, although larger studies are necessary to confirm these results.

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