

Short Duration versus 14-day Antibiotic Treatment in Acute Cholangitis due to Bile Duct Stone: A randomized study

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ABSTRACT

BACKGROUND AND AIMS: The optimal duration of antibiotic therapy in common bile duct stone associated cholangitis is not well established. We aimed to assess the efficacy and safety of short duration vs 14-day antibiotic therapy in acute cholangitis associated with common bile duct stone.

METHODS: Eighteen (9 mild cholangitis and 9 moderate cholangitis) were recruited in group A (antibiotic cessation when fever subsided for 72 hours) and 16 (8 mild cholangitis and 8

moderate cholangitis) were recruited in group B (a full 2 weeks of antibiotic therapy). Both groups were evaluated and compared in term of the recurrence rate, duration of fever, abdominal pain, hospital stay and complications. The duration of antibiotic therapy in group A and in patients with or without bacteremia were evaluated and compared.

RESULTS: No recurrence occurred in group A and 1 recurrence occurred in group B ($p = 0.485$). Clinical outcomes were similar between the 2 groups. The fever duration was similar between mild and moderate cholangitis within the same group and between the 2 groups. Duration of antibiotic therapy in group A was 4.61 ± 1.37 days with 16 (88%) needing treatment for ≤ 5 days. The duration of treatment was similar between patients with or without bacteremia. The hospital stay was similar in both groups and no complications occurred.

CONCLUSIONS: Short duration antibiotic therapy based on fever resolution of 72 hours was effective and safe in patients with mild to moderate cholangitis due to common bile duct stone.

Key words: Common bile duct stone; Cholangitis; Antibiotic; Bacteremia; Biliary drainage

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BACKGROUND

Acute cholangitis is a potentially life-threatening condition^[1]. Biliary tract obstruction, from stone or either benign or malignant bile duct stricture, followed by biliary bacterial colonization are the two main factors in the pathogenesis of acute cholangitis^[1,2]. Biliary drainage and systemic antibiotics (ATB) are crucial for the management of

cholangitis and endoscopic retrograde cholangiopancreatography (ERCP) is the accepted drainage procedure^[1,3]. The optimal duration for ATB administration in cholangitis is not well established^[1,4]. To the best of our knowledge, there are four published studies pertaining to the duration of ATB administration and one study switching intravenous ATB to oral form after biliary drainage in acute cholangitis^[5,9]. One small uncontrolled study^[5] reported that discontinuing the antibiotic when fever subsided for 24 hours in patients with moderate to severe cholangitis was safe and effective; all of the cholangitis cases in this study except one were associated with biliary stone. Three other studies^[6,8] were retrospective studies and included patients with stone and both benign and malignant strictures. For a biliary stone, complete removal of the stone may provide more effective biliary drainage. In contrary, the criteria for adequate biliary drainage in biliary strictures are usually defined as total bilirubin declining > 50% of the initial value^[10,11] rather than the complete resolution of jaundice and this may leave some patients only partially drained.

We aimed to study the efficacy and safety of antibiotic administration based on the time of fever resolution as the stopping point compared with standard 2-week antibiotic therapy in common bile duct (CBD) stone associated cholangitis where complete drainage of biliary tree by complete stone clearance can be achieved with more confidence.

MATERIALS AND METHODS

Patients and ethics

This study was approved by the Faculty of Medicine Ethics Committee (study protocol no. 56-124-21-12) and was conducted in accordance with the ethical standards of the institution research committee and the Helsinki Declaration. The study was registered at Clinical Trials.gov with the registration number NCT 02666820. Patients aged more than 18 years with the diagnosis of acute cholangitis by the Tokyo Guidelines criteria^[12] associated with common bile duct stone (CBDS) were enrolled from August 2017 to August 2018. Patients with severe cholangitis based on Reynold's Pentad^[13] were excluded due to Ethics Committee concerns regarding the safety of patients. ERCP for biliary drainage was performed on all patients within 72 hours after admission. Exclusion criteria included patients with acute cholangitis due to other causes, pregnant patients, and patients with concomitant acute calculous cholecystitis, with concomitant intrahepatic bile duct stones, with bile duct stricture, with severe co-morbidity, with surgically altered anatomy, with active concomitant infection of other organs, with a concomitant emergency situation, with uncorrected coagulopathy, with a cephalosporin allergy, or who declined to participate in the study. Informed consent was obtained from each patient prior to entry to the study

Study Protocol

The participating patients were randomized to receive short duration of ATB (group A) (antibiotic cessation when fever subsided for 72 hours), or the standard 14 days of ATB (group B). Complete blood count (CBC), prothrombin time (PT), liver function test (LFT), renal function test, and imaging by abdominal ultrasonography (US) and/or computed tomography (CT) were done in all patients. After blood samples were collected for bacterial culture and susceptibility testing, intravenous ATB therapy was immediately begun. Randomization codes were generated by a computer using a random mixing box (combination box set) and concealed in envelopes. Once biliary

cannulation was achieved and CBDS was confirmed, the patients were randomized to the treatment arms noted above.

Antibiotic protocol

The ATB used in this study was ceftriaxone 2 gram intravenously once daily based on the consensus statement of antimicrobial therapy of intra-abdominal infections in Asia^[14]. Antipyretics were not allowed during the admission period of the study. In group A, intravenous ATB was discontinued when the body temperature (BT) was less than 38°C for 72 hours. In group B, intravenous ATB was administered for 7 days followed by oral ciprofloxacin 500 mg. twice daily for an additional 7 days regardless of BT. Patients were discharged when their clinical condition was stable at the discretion of the attending physician and the patients in group B continued the ATB according to the protocol on the out-patient basis. Patients with persistent BT > 38°C longer than 4 days following the first dose of intravenous ATB were evaluated for complications of acute cholangitis and infection of the other organs where appropriate.

Intervention

The ERCP procedures were done by a trainee under supervision or by a staff doctor within 72 hours after admission. The ERCP was performed with the patient in the prone position using a side view duodenoscope (Olympus Model TJF-160 R/JF-140 R) under the standard protocol in our institute of conscious sedation with intravenous midazolam, pethidine and/or propofol^[15]. After successful common bile duct (CBD) cannulation with CBDS confirmed, bile samples were obtained for bacterial culture and sensitivity testing. Endoscopic sphincterotomies were done using an ERBE 200 D© with Endocut I® with the settings of a 2-second cutting duration, a 3-second cutting interval, effect 2 and max watts 60. Stone extractions were carried out by a stone retrieving balloon or a basket at the discretion of the endoscopist who performed the ERCP until complete CBDS clearance was achieved. Complete stone clearance was defined as no filling defect detected by the final occluded cholangiogram. In patients with incomplete CBDS clearance, a plastic double-pigtail biliary stent (7 or 10 Fr.) was placed at the discretion of the endoscopist.

Follow up

The vital signs were recorded every 6 hours. Blood cultures, CBCs and LFTs were performed at day 1 after the ERCP. Follow-up visits for clinical symptoms assessment and LFTs were scheduled at 1, 2, 4 and 8 weeks after discharge. For patients who defaulted, the information regarding their clinical status was obtained by a telephone call to the patient or a relative. All patients were advised to contact the principle investigator if they had recurrent fever, jaundice, or abdominal pain.

Outcome measurements

The primary outcome was the recurrence rate of cholangitis after the discontinuation of ATB therapy. Recurrent cholangitis was defined as recurrence of fever (BT > 38°C) with no other source of infection identified. The secondary outcomes were recurrence rate of cholangitis in complete stone clearance compared with incomplete clearance groups, clinical and laboratory parameters within 24 hours after ERCP, duration of fever, duration of antibiotic therapy in group A, the outcome of patients with bacteremia compared to patients without bacteremia, duration of hospital stay and the number of complications. Procedure-related complications were defined according to the consensus criteria^[16].

Table 1 Base line demographic data, abdominal pain intensity, concomitant gallstone, CBD diameter and laboratory data of the two study groups.

	Group A	Group B	P-value
Total patients (male/female)	18 (11/7)	16 (10/6)	0.934
Age, mean (SD), years	71.6 (16.1)	69.7 (16.7)	0.735
Cholangitis severity mild/moderate	9/9	8/8	1.0
Abdominal pain score before ERCP, mean (SD), score 0 – 10	7.53 (3.56)	7.38 (3.54)	0.901
Common bile duct diameter, mm, mean (SD)	8.94 (4.09)	10.37 (3.96)	0.285
Concomitant gallstone, n	11	12	0.385
Total bilirubin, mean (SD), mg %	5.17 (6.47)	8.9 (13.3)	0.325
AST, mean (SD), U/L	371 (509)	208 (319)	0.269
ALT, mean (SD), U/L	206 (177)	142 (188)	0.317
ALP, mean (SD), U/L	314 (233)	332 (226)	0.817
Hemoculture positive	6	4	0.595
Escherichia coli	5	4	
Klebsiella pneumonia	1		

AST: Aspartate Aminotransferase; ALT: Alanine Aminotransferase; ALP: Alkaline Phosphatase.

Statistical analysis

Sample size

A previous study found the incidence of recurrent cholangitis associated with CBDS after biliary drainage was 3.8%^[17]. Calculations using the Epidemiological Calculator (R package version 2.14.1.6) based on non-inferiority between two groups with a difference of recurrent cholangitis less than 15% between groups with the following parameters, Alpha = 0.05, power = 0.8, proportion = 0.038 and significant inferior (level of reduction of effectiveness as being clinically significant) = 0.15, gave a required sample size in each group of 21 and thus a total number of 42. Allowing for an approximately 10% drop-out rate, the number of participants needed for this study was 46.

Baseline characteristic data of the patients were expressed in mean and standard deviations for continuous variables and in percentages for discrete variables. Comparisons between the two groups were assessed by Student *t*-test for parametric data and Chi-square or Fischer’s exact test for nonparametric data. A P-value of less than 0.05 was considered as statistically significant.

RESULTS

Due to the slow recruiting rate during the study period, the enrollment was terminated with 36 patients enrolled (85% of calculated sample size). Two patients were excluded from analysis, one with concomitant intrahepatic duct stone and the other with a bile duct stricture, leaving 34 patients for analysis. Thirty-two patients completed the 8-week study period. There was no patient defaulted in group A but there were 2 patients defaulted at week 8 in group B. The follow-up information of the defaulted patients regarding clinical symptoms and LFT done elsewhere were obtained by telephone interview (Figure 1).

Group A had 18 patients, 11 males and 7 females, with 9 cases of mild cholangitis and 9 cases of moderate cholangitis, Group B had 16 patients, 10 males and 6 females, with 8 cases of mild cholangitis and 8 cases of moderate cholangitis. The baseline demographic data, abdominal pain intensity, CBD diameter, number of patients with concomitant gallstones and LFT were not significantly different between the 2 groups. There were 6 patients with bacteremia in group

Table 2 Time from admission to ERCP and clinical parameters after ERCP.

	Group A	Group B	P-value
Duration from admission to ERCP, hours, mean (SD)	18.4 (14.6)	22.8 (14.7)	0.395
ERCP within 24 hours	15	10	
ERCP within 48 hours	2	6	
ERCP within 72 hours	1	0	0.167
Abdominal pain score 24 hours after ERCP, 0-10 score, mean (SD)	1.56 (1.76)	1.50 (1.32)	0.917
Duration of fever after ERCP, days, mean (SD)	1.83 (1.29)	1.94 (1.77)	0.848
Duration of fever after ERCP in mild cholangitis, mean (SD)	1.11 (0.35)	1.63 (1.77)	0.445
Duration of fever after ERCP in moderate cholangitis, mean (SD)	1.67 (0.86)	1.88 (1.13)	0.69

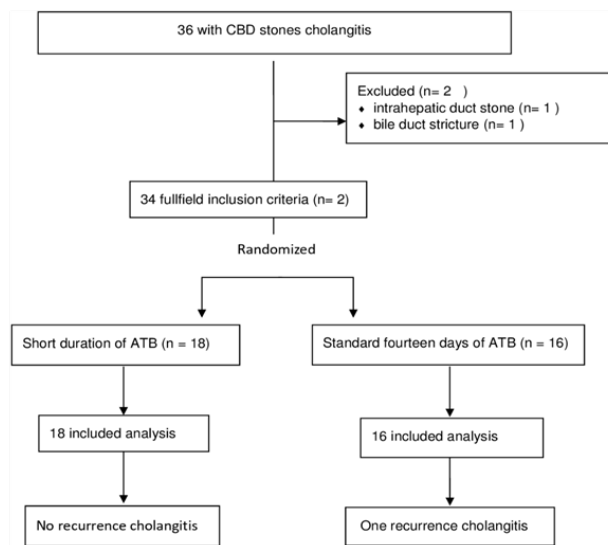


Figure 1 Flow of patients through the study.

A and 4 patients with bacteremia in group B ($p = 0.595$) (Table 1). The bacterial species isolated in blood are shown in table 1. Twenty-two patients (65%) had bile culture done, which were positive in all 12 patients in group A and in 8 of 10 patients in group B ($p = 0.194$).

Interval from admission to ERCP drainage

The mean \pm SD duration from admission to ERCP drainage was 18.4 \pm 14.6 and 22.8 \pm 14.7 hours in group A and group B, respectively, and the difference was not statistically significant ($p = 0.395$). Biliary drainage was done within 24 hours in 15 patients, 48 hours in 2 patients and 72 hours in 1 patient in group A and within 24 hours in 10 patients and 48 hours in 6 patients in group B, however the difference was not statistically significant (Chi square $p = 0.167$).

Primary outcome

Recurrent rate of cholangitis

There were no cases of recurrent cholangitis in group A and one case in group B at 2 weeks after ERCP ($p = 0.485$). The rest of the patients in both groups had no recurrent cholangitis throughout the 8 weeks of follow-up.

Secondary outcomes

There were 2 patients with incomplete stone clearance, one in group A and one in group B, so statistical analysis was not done, as such a small number of patients precluded any meaningful results. Both

patients underwent a second ERCP with complete stone clearance.

The abdominal pain intensity scores within 24 hours after ERCP were not significantly different between the 2 groups (Table 2).

The mean \pm SD duration of fever after ERCP was 1.83 ± 1.29 and 1.94 ± 1.77 days in group A and group B, respectively, and the difference was not significant ($p = 0.848$). The mean \pm SD days for fever in group A in mild cholangitis was 1.11 ± 0.35 compared with 1.67 ± 0.86 in moderate cholangitis, and in group B, the mean \pm SD days of fever in mild cholangitis was 1.63 ± 1.77 and 1.88 ± 1.13 in moderate cholangitis. However, the differences were statistically not significant ($p = 0.103$ and $p = 0.742$ respectively). The mean duration of days of fever in mild cholangitis in group A was not significantly different from that of mild cholangitis in group B ($p = 0.445$), and neither was the mean duration of days of fever in moderate cholangitis in group A compared with group B ($p = 0.69$).

The mean \pm SD duration of ATB therapy in group A was 4.61 ± 1.37 days with a range of 3 to 9 days. Sixteen of 18 patients (88%) in group A required antibiotic treatment for ≤ 5 days. The mean \pm SD days of antibiotic treatment in mild cholangitis was 4 ± 0.70 while it was 5.2 ± 1.64 in moderate cholangitis, which indicated a trend of longer duration of treatment in moderate cholangitis than in mild cholangitis ($p = 0.067$). There was no significant difference in mean duration of ATB therapy between the 6 patients with bacteremia and the 12 patients without bacteremia (4.50 ± 0.548) vs (4.67 ± 1.67) days respectively, $p = 0.758$). All patients with bacteremia had negative blood cultures 24 hours after the initial ERCP.

The mean \pm SD days of hospital stay in group A was 5.78 ± 2.39 and in group B was 6.38 ± 2.33 , but the difference was not significant (Student t test, $p = 0.467$).

Complications

None of the patients in either group developed ERCP-related complications.

DISCUSSION

This randomized study demonstrated that discontinuation of ATB 72 hours after abatement of fever was as effective and safe as the standard fourteen days of ATB treatment in patients with mild to moderate cholangitis related to a CBD stone. None of our patients in group A developed recurrence cholangitis after discontinuation of the ATB treatment. The mean duration of intravenous ATB after complete CBDS clearance in our study was 4.61 days with a range of 3 to 9 days and 88% of our patients required the antibiotic for ≤ 5 days. The hospital stays were not different between the two groups because we treated the patients in group B on an out-patient basis, however, we did not analyze the cost of treatment of both groups, and the cost of travel to the hospital for the ATB injection in group B, which may incur more expense than in group A. In a prospective case series study of 18 patients with cholangitis, 17/18 associated with stone, reported by Kogure H *et al*^[5], the median duration of ATB treatment was 3 days; however, in this study the ATB administration was discontinued when the fever had subsided for 24 hours which may account for shorter duration of ATB treatment compared to our study. Biliary drainage was done by stent insertion or nasobiliary drainage tube in the study of Kogure H *et al*^[5], suggesting that drainage by these methods is adequate for acute cholangitis associated with CBDS. Van Lent *et al* found in a retrospective study that a short 3-day duration ATB was safe and effective when the time interval between onset of cholangitis and biliary drainage was short, adequate drainage was achieved and the fever was abating. However, their recurrent cholangitis rate was 27%, which was much higher than in

our study^[6]. The population in the study of Van Lent *et al*^[6] included cholangitis from stone and benign as well as malignant stricture where complete drainage could not be achieved in every patient leading to a higher recurrence rate. Fifteen of 18 patients in group A had biliary drainage done within 24 hours in our study and the study by Kogure H *et al*^[5] biliary drainage was done within 24 hours. Our study and the study of Kogure H *et al*^[5] used fever resolution as the time of ATB discontinuation whereas the other studies did not clearly define their criteria^[6-8]. Bacteremia occurred in 10 patients in our study, 6 of 10 patients in group A and 4 of 10 patients in group B, but the bacteremia had no influence on the outcome of the short duration ATB treatment. Furthermore, all the blood cultures of the bacteremia patients were negative at 24 hours after complete stone clearance. The study of Kogure H *et al*^[5] had the same result and this may underscore the crucial role of biliary drainage in rapid resolution of bacteremia in acute cholangitis. Doi A *et al*^[8] reported in a retrospective study that short-term TB treatment of ≤ 7 days with a median duration of 6 days with a range of 2-7 days for patients with cholangitis and bacteremia was as safe and effective as the longer duration ATB treatment. Another retrospective study by Uno S *et al*^[7] found that ATB treatment for ≤ 14 days did not increase the risk of failure in patients with acute cholangitis and bacteremia. Despite these limitations of the current data, all the data suggest that short course ATB treatment is safe and effective in cholangitis with all grades of severity with or without bacteremia provided that adequate drainage was performed promptly, and these findings conformed to the 4-7 days of ATB therapy as recommended by TG 18^[4]. Further randomized studies with adequate numbers of patients to substantiate these findings are required.

There were some limitations in our study. First, the study was a single center study, and enrolled only patients with CBDS cholangitis, therefore, the results may not be generalizable to patients in different settings. Second, our study included only mild to moderate cholangitis, thus our findings may not be applicable to patients with severe cholangitis, even though at least one study has suggested that the short-term treatment may be feasible for these patients^[5]. Third, the number of patients enrolled was less than the calculated sample size due to difficult recruitment, so it might be underpowered.

In conclusion, our prospective study suggests that short duration ATB therapy using a fever resolution of 72 hours as a safe time to discontinue the ATB for acute CBDS cholangitis with or without bacteremia after successful endoscopic biliary drainage is safe and effective. The expense incurred by treatment, the risk of organisms developing resistance as well as the risk of developing antibiotic-associated complications will be reduced by shorter duration of ATB administration.

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