Original Article

THAI J GASTROENTEROL 2014
Vol. 15 No. 3
Sep. - Dec. 2014
155

A Randomized Controlled Trial Comparing between Short Duration and Standard 14 days of Antibiotic Treatments for Acute Cholangitis in Patients with Common Bile Duct Stone after Successful Endoscopic Biliary Drainage

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ABSTRACT

Background & Aims: To compare the efficacy and safety of short duration with standard 14 days of antibiotic treatment in patients with acute cholangitis due to common bile duct stone (CBDS) after successful endoscopic biliary drainage.

Methods: A prospective randomized study of patients with mild to moderate acute cholangitis due to CBDS with symptoms duration of 48 hours or less. The patients were randomized at the time of ERCP to a short duration (group A) or a standard fourteen days of antibiotic treatment (group B) from February 2013 to November 2013. Ceftriaxone was used as the antibiotic therapy in both groups. The endoscopic drainage by ERCP was done within 72 hours after admission. The complete endoscopic drainage was defined when all the CBDSs were removed and the incomplete endoscopic drainage was defined when some residual stones were present and the stent insertion was needed. In the short duration treatment group, antibiotic was stopped when the patient was afebrile for 72 hours.

Results: A total of 16 patients (7 female and 9 male) with the mean age of 69.8±15.4 years were recruited. There were eight patients in group A and B. The demographic data, the abdominal pain intensity, liver function test (LFT) and number of CBDS were not significantly different between the 2 groups. The clinical responses including duration of fever, abdominal pain, improvement of LFT, and the number of patient with incomplete drainage after treatment were similar between group A and B. The mean ± SD duration of antibiotic treatment in group A was 5 ± 1.7 days with a range of 4-9 days. There were 3 patients with bacteremia in each group but none of patients in both groups developed recurrent cholangitis after 2 months of follow-up.

Conclusions: This data suggested that short duration antibiotic therapy for acute CBDS cholangitis after successful endoscopic biliary drainage was safe and effective as the standard fourteen days antibiotic treatment.

Key words : Acute cholangitis, common bile duct stone, ERCP, drainage

[Thai J Gastroenterol 2014; 15(3):155-159.]

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INTRODUCTION

Acute cholangitis is a potentially fatal condition, characterized by acute inflammation and bacterial infection of biliary system[1]. The major pathogenesis of acute cholangitis are biliary obstruction and ascending bacterial infection in the bile duct[2]. The principles of treatment are appropriate biliary drainage and systemic antibiotics (ATB). Endoscopic retrograde cholangiopancreatography (ERCP) is generally accepted as standard technique for biliary drainage due to its less invasiveness while providing favorable outcome when compare to percutaneous and surgical approach[3]. The traditional duration of the antibiotic therapy is 7-10 days despite promptly clinical response to biliary drainage. The appropriate duration of the antibiotic therapy following adequate biliary drainage is currently unknown[4-5]. To our knowledge, there are only two published studies focusing in the duration of antibiotics therapy after successful endoscopic drainage in acute cholangitis. The limitations of these two studies are: one study was retrospective and included heterogeneous group of patients, the adequacy of drainage was not clearly stated and the result showed very high recurrent rate of ascending cholangitis[5]; the other study had a small number of patients and was not a comparative study6. Because unnecessarily prolonged use of antibiotic may predispose to adverse reactions and facilitate the development of antibiotic resistant bacteria, it is preferable to discontinue antibiotics as soon as possible.

Therefore, we conducted the present study to determine the efficacy and safety between short duration compares with standard fourteen days antibiotic treatment in patients with acute common bile duct stone (CBDS) cholangitis after successful endoscopic biliary drainage.

MATERIAL AND METHODS

Patients

Patients with the age of 18 years or more, diagnosis of mild to moderated acute cholangitis caused by CBDS, and the biliary drainage by ERCP could be performed within 72 hours after admission were included in the study. The exclusion criteria were pregnancy, the causes of cholangitis was not CBDS, patients with severe co-morbidity, active concomitant infections of the other organs, allergy to cephalosporin antibiotics, and who cannot give the informed consent. Acute ascending cholangitis is defined according to Tokyo guidelines 2007[1]. Severity: mild to moderate severity of acute ascending cholangitis is defined by absent of Reynolds' pentad (Charcot's triad plus shock and a decreased level of consciousness)[1]. Recurrent cholangitis is defined by recurrent of fever after complete therapy without other sources identified.

Study Protocol

All eligible patients were obtained informed consent. Patients were randomized to receive short duration of antibiotic (group A) or standard fourteen days of antibiotics (group B). The complete blood count (CBC), prothrombin time (PT), liver function test (LFT), renal function test, C-reactive protein (CRP), and abdominal ultrasonography or computed tomography were done in all patients. After collected blood samples for culture and susceptibility test, the intravenous antibiotic therapy was immediately administered. The randomization codes were generated by the computer using a random mixing box (combination box set), and concealed in envelops. Once the biliary cannulation was achieved, the concealed randomization code was open by the investigator who was blinded to the treatment results. The vital signs were recorded every 6 hours. The body temperature was measured by a thermometer at axilla. At day 1 and 7 after ERCP with biliary drainage, blood sample were collected to evaluate.

Antibiotic protocol

The antibiotic of choice in this study was ceftriaxone 2 gram intravenously every 24 hour, based on the consensus statement of antimicrobial therapy of intra-abdominal infections in Asia7. The antipyretics were not allowed during the study. In group A, the intravenous antibiotic was discontinued when the body temperature was less than 37.8 ˚C for 72 hours. In group B, the intravenous antibiotics for 7 days followed by the oral antibiotics for 7 days were given regardless of body temperature. In patients who had prolonged fever of more than 37.8 ˚C for 4 days or more since the first dose of intravenous antibiotic, the complications of acute cholangitis (eg. liver abscess) and the infection at the other organs were evaluated.

Intervention

The ERCP under conscious sedation was per-

formed within 72 hours after diagnosis of acute cholangitis by experienced endoscopists. The therapeutic duodenoscope (Olympus) was used in this study. After successful common bile duct (CBD) cannulation, bile was aspirated for culture and sensitivity test, and low-osmolality, non-ionic contrast medium was carefully injected into the bile duct. Endoscopic sphincterotomy and stone extraction were carried out until completion of CBDS clearance. In patients with incomplete CBDS clearance, a plastic biliary stent (7 or 10 Fr) was placed into CBD.

Follow up

Patients were evaluated at the outpatient clinic at 1, 4, and 8 weeks. If patients missed their appointments, the information regarding current status was obtained by a telephone call to the patients or their relatives. All patients were advised to contact the principle investigator if they had recurrent fever, jaundice, or abdominal pain.

Outcome measurement

The primary endpoint of the study is the recurrent rate of acute cholangitis. The secondary endpoints of the study are adequacy of drainage and outcome of therapy, the overall morbidity and mortality relate to acute cholangitis.

Statistical analysis

Baseline descriptive data were expressed in mean and standard deviations for continuous variables and in percentages for discrete variables. Comparisons between two groups were assessed by Student *t*-test for parametric data and Wilcoxon rank-sum test for non-parametric data. Proportional data were assessed by Chi-square or Fischer's exact test. *P*-valve of less than 0.05 was considered statistically significance.

Results

During the study period, 16 patients were recruited to the study. Eight were in group A and eight in group B. The baseline demographic data, the abdominal pain intensity, LFT and number of CBDS were not significantly different between the 2 groups (Table 1). The clinical response including duration of fever, abdominal pain, improvement of LFT, and the number of patient with incomplete drainage after treatment were similar between group A and B (Table 2 and 3). The mean ± SD duration of ATB in group A was 5 ±1.7 days (range 4-9 days) significantly different from group B ($p<0.001$). There were 3 patients with bacteremia and 1 patient with incomplete biliary drainage in each group but none of patients in both groups developed recurrent cholangitis after 2 months of follow-up (Table 3).

Table 1. Comparison of background demographic data between group A and B.

	Group A	Group B	*p* -value
Total patient, n	8	8	-
Sex (male/female), n	5/3	5/3	-
Age [mean (SD)], years	73.1 (15.9)	66.5 (15.3)	0.41
Abdominal pain score before ERCP [mean (SD)], 0 - minimum, 10 - maximum	9.1 (1.8)	8.8 (1.5)	0.657
WBC count [mean (SD)], cells/mL	15893.8 (11017.3)	8912.5 (2918.7)	0.105
AST [mean (SD)], U/L	322.6 (464)	249.9 (447)	0.754
ALT [mean (SD)], U/L	183.6 (128.2)	191.5 (254.7)	0.939
ALP [mean (SD)], U/L	311.9 (281.8)	349.9 (259.4)	0.783
Total bilirubin [mean (SD)], mg%	4.6 (1.3)	8.9 (15.5)	0.448
Positive hemoculture before ERCP, n (%)	3 (37.5)	3 (37.5)	1
Presence of gallstone by U/S, n (%)	4 (50)	5 (62.5)	1
Presence of CBDS by U/S, n (%)	4 (50)	3 (37.5)	1
Presence of CBD dilatation by U/S, n (%)	7 (85.7)	7 (85.7)	1

*Group A: short duration, Group B: traditional 14-day

Table 2. Comparison of clinical response at 24 hours after ERCP.

	Group A	Group B	*p* -value
Adequacy of drainage (complete/partial), n (%)	7 (85.7)/1 (14.3)	7 (85.7)/1 (14.3)	1
Duration from admission to ERCP [mean(SD)], hours	21.2 (21)	24.2 (13.9)	0.742
Abdominal pain score after ERCP [mean (SD)], 0 - minimum, 10 - maximum	2.2 (2.1)	1.4 (1.2)	0.326
Duration of fever after ERCP [mean(SD)], hours	1.8 (1.8)	1.2 (0.7)	0.467
Duration of antibiotics [mean (SD)], days	5 (1.7)	14 (0)	<0.001
WBC count [mean (SD)], cells/mL	9412.5 (2806.5)	8978.8 (3114.7)	0.774
AST [mean (SD)], U/L	45.9 (24.1)	50.6 (17.3)	0.657
ALT [mean (SD)], U/L	78 (45)	88 (62)	0.718
ALP [mean (SD)], U/L	249.6 (179)	294.5 (155.8)	0.601
Total bilirubin [mean (SD)], mg%	2.5 (1.7)	7.7 (14.5)	0.332
Positive hemoculture after ERCP, n (%)	0 (0)	0 (0)	1

*Group A: short duration, Group B: traditional 14-day

Table 3. Comparison of clinical at the follow up periods.

	Group A	Group B	*p* -value
Total bilirubin after drainage 7 days [mean (SD)], mg%	1.3 (0.6)	2.7 (4.2)	0.37
Total bilirubin after drainage 14 days [mean (SD)], mg%	0.8 (0.4)	1 (0.2)	0.499
Cholangitis after ERCP 7 days, n (%)	0(0)	0(0)	1
Cholangitis after ERCP 14 days, n (%)	0(0)	0(0)	1
Cholangitis after ERCP 28 days, n (%)	0(0)	0(0)	1
Cholangitis after ERCP 56 days, n (%)	0(0)	0(0)	1

*Group A: short duration, Group B: traditional 14-day

In group A after withdrawal of ATB, no recurrent cholangitis or CBDS-related complications occurred; subsequently no need for re-administration of ATB. During the follow up period of eight weeks, none of the patients in both group developed recurrent cholangitis or CBDS-related complication. No minor or major early ERCP-related complication was found in this study.

DISCUSSION

To date, this is the first open-labeled, randomized controlled study comparing the duration of ATB between short duration and traditional fourteen days in acute mild to moderate CBDS cholangitis after successful endoscopic biliary drainage. The preliminary data demonstrated that the short duration antibiotic therapy was as safe and effective as the traditional fourteen days of antibiotic treatment. The duration of intravenous ATB after complete CBDS clearance in our study is similar to previous studies by van Lent *et al*[5] (median duration of ATB 3 days: range 0-42 days) and Kogura *et al*[6] (median duration of ATB 2 days: range 1-6 days). None of the patients developed recurrent cholangitis or CBDS-related complication after discontinuation of the antibiotic treatment.

The guideline[1] recommends the duration of ATB administration for 5-7 days in patients with acute cholangitis but there is little evidence supports this recommendation. Our preliminary showed that after successful drainage, continuation of ATB for three days after afebrile were safe and efficacy, which was confirmed in previous prospective study[6].

Special concern in acute cholangitis is bacteremia. The duration of ATB administration is recommended for 7-10 days in patients with bacteremia, according to the surviving sepsis campaign guideline[11]. However, the major pathogenesis of acute cholangitis and bacte-

remia is biliary obstruction[2]. The present study found bacteremia in 6 patients (three in each groups), none of these patients developed sepsis related-complication during follow period up to eight weeks after stop ATB. Furthermore, the hemoculture at 24 hours after biliary drainage turned to negative results in all six patients who had positive hemoculture before ERCP. The results suggested that early bacteremia in acute cholangitis would be transient if the obstruction was successfully relieved, and the short duration of ATB treatment will be safe and sufficient in this setting.

There were limitations in the present study. First, the sample size of 8 patients in each groups were too small to provide adequate power. This preliminary result revealed that there was no patient developed recurrent cholangitis and the final conclusion would be conducted after complete of the study. Second, our study included only mild to moderate cholangitis, in severe cases who had Raynaud pentad (hypotension or alteration of consciousness) the short duration ATB might not be applicable.

In conclusion, our preliminary data suggested that short duration antibiotic therapy for acute CBDS cholangitis after successful endoscopic biliary drainage would be as safe and effective as the traditional fourteen days antibiotic treatment.

Acknowledgement

The authors would like to gratefully thank the patients in this study and all volunteers including other staffs from nearby hospitals that referred patients to our center. This work was partial supported by Gastroenterological Association of Thailand Research Grant.

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