Prospective comparison of prophylactic antibiotic use between intravenous moxifloxacin and ceftriaxone for high-risk patients with post-ERCP cholangitis

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BACKGROUND: The use of prophylactic antibiotics before endoscopic retrograde cholangiopancreatography (ERCP) is recommended by all major international gastroenterological societies, especially in the presence of an obstructed biliary system. This study compared the occurrence rate of post-procedural complications, including cholangitis and septicemia, between prophylactic intravenous moxifloxacin and ceftriaxone in patients with bile duct obstruction scheduled for therapeutic ERCP.

METHODS: From November 2013 to July 2015, 86 consecutive patients with biliary obstruction with one or more factors predicting benefits of antibiotic prophylaxis prior to ERCP were included in the current randomized open-label non-inferiority trial (ClinicalTrial.gov identifier NCT02098486). Intravenous moxifloxacin (400 mg/day) or ceftriaxone (2 g/day) were given 90 minutes before ERCP, and were administered for more than 3 days if the patient developed symptoms and signs of cholangitis or septicemia. Recalcitrant cholangitis was defined as persistence of cholangitis for more than 5 days after ERCP or recurrence of cholangitis within 30 days after ERCP.

RESULTS: Recalcitrant cholangitis occurred in 1 (2.3%) and 2 (4.8%) patients receiving intravenous moxifloxacin and ceftriaxone group, respectively (P=0.612). Septicemia was noted in 1 (2.3%) and 1 (2.4%) patient in intravenous moxifloxacin and ceftriaxone group, respectively (P=1.0). The mean hospital stay was also not significantly different between the moxifloxacin and ceftriaxone groups (8.8±7.2 vs 9.1±9.4 days, P=0.867). Antibiotic resistance of the isolated pathogens by *in vitro* activity assay was noted in 1 (2.3%) and 2 (4.8%) patients in the moxifloxacin and ceftriaxone group, respectively (P=0.612).

CONCLUSION: Intravenous moxifloxacin is not inferior to intravenous ceftriaxone for the prophylactic treatment of post-ERCP cholangitis and cholangitis-associated morbidity.

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KEY WORDS: endoscopic retrograde cholangiopancreatography; cholangitis; moxifloxacin; ceftriaxone; recalcitrant cholangitis

Introduction

Endoscopic retrograde cholangiopancreatography (ERCP) is a standard diagnostic and therapeutic modality in pancreatobiliary disorders.[1, 2] Bile duct obstruction caused by various disorders like choledocholithiasis, and benign or malignant stricture can lead to increased intra-biliary pressure with cholangio-venous reflux and bacteremia, which may progress to septicemia.[3] In the presence of an obstructed bile duct, biliary decompression by endoscopic sphincterotomy, stone extraction, stent insertion, and balloon dilatation are essential therapeutic techniques which can restore free biliary drainage.[4, 5] The risk of precipitating cholangitis or septicemia during these procedures is much greater than in simple diagnostic ERCP.[6-8]

A recent guideline recommended that antibiotic prophylaxis could be considered before an ERCP only in patients with known or suspected biliary obstruction, where there is a possibility that complete drainage may

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not be achieved at the ERCP, such as occurs in patients with a hilar stricture and primary sclerosing cholangitis.[9] However, the strength of evidence for this recommendation was weak. A recent systematic review and meta-analysis indicated that administration of antibiotics prior to elective ERCP can reduce the risk of bacteremia, cholangitis, septicemia, and pancreatitis.[1, 10] Thus, the available data regarding the clinical significance of prophylactic antibiotics preceding ERCP are inconsistent. Another limitation in evaluating an optimal prophylactic antibiotic strategy is the variation in antibiotics used prior to ERCP procedures. The aforementioned-studies used various kinds of antibiotics in practice. Hence, it is not possible to determine which antibiotic may provide prophylactic effects. Although the optimum prophylactic antibiotics for ERCP are not yet determined, the recommendations of recent guidelines and its once-daily administration, has made ceftriaxone the most frequently prescribed antibiotic in patients with bile duct obstruction prior to therapeutic ERCP.

Moxifloxacin is a newly marketed fourth-generation fluoroquinolone antibiotic with a broad spectrum of antibacterial activity against Gram-positive and Gram-negative aerobic and anaerobic bacteria.[11-13] It has excellent microbiological activity against common pathogens found in biliary tract infection.[12-14] Moxifloxacin displays significant biliary excretion and sufficient bactericidal concentrations above minimal inhibitory concentrations for most expected bacteria in biliary tract infection even in patients with an obstructed bile duct.[12, 15, 16] Based on these reasons, we speculated that moxifloxacin might be an effective prophylactic antibiotic prior to therapeutic ERCP to reduce the occurrence rate of post-procedural complications after endoscopic biliary drainage.

This randomized open-label non-inferiority study addressed this speculation by comparing the prophylactic efficacy of intravenously administered moxifloxacin and ceftriaxone in reducing the occurrence of post-procedural complications, including cholangitis, bacteremia and septicemia in patients with bile duct obstruction scheduled for therapeutic ERCP.

Methods

Study population

This study enrolled patients with bile duct obstruction who underwent therapeutic ERCP at our institution from November 2013 to July 2015 (ClinicalTrial.gov identifier NCT02098486).

The inclusion criteria were as follows: 1) age from 19 to 90 years old; 2) bile duct obstruction because of choledocholithiasis, and benign or malignant bile duct stricture; 3) drainage was incomplete or difficult due to complex anatomical structure or underlying diseases, such as hilar cholangiocarcinoma, and primary sclerosing cholangitis; 4) symptoms and signs of cholangitis and complete biliary obstruction.

The exclusion criteria were as follows: 1) pregnancy; 2) history of hypersensitivity to moxifloxacin or ceftriaxone; 3) previous antibiotic exposure of any kind or theophylline derivatives medication within 14 days of admission; 4) previous history of epilepsy; 5) previous history of infective endocarditis due to valvular heart disease; 6) ongoing active anticoagulant treatment.

Among the 109 patients, 12 with previous antibiotic treatment because of other definite infections before ERCP were excluded. The remaining 97 patients were randomly allocated to either moxifloxacin or ceftriaxone group. For these 97 initially randomized patients, 11 were excluded from the final analysis because of the following reasons: an attending endoscopist failed in cannulation of bile duct and in obtaining cholangiogram (n=6), only a simple diagnostic procedure was performed (n=2), and relevant clinical data were incomplete (n=3). The final numbers of eligible subjects were 44 in the moxifloxacin group and 42 in the ceftriaxone group (Fig.). Randomization was done using consecutively numbered computer-generated cards containing treatment assignment (https://www.randomizer.org/). We adopted "simple randomization" for random allocation of our enrolled patients to each antibiotic group. "Randomization" database was password-protected and accessible only by principal investigator.

Before participation, patients were fully informed of the objective and methods of this clinical trial, and potential benefits and risks of participation. Only then they were provided written informed consent for participation. The study protocol was approved by the Ethics

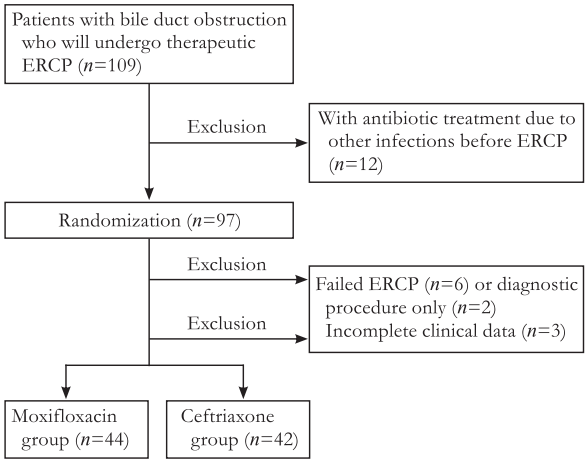

Fig. Flow diagram illustrating the selection of study subjects.