Original Article

Intravenous Ciprofloxacin vs. Ceftriaxone for The Prevention of Bacterial Infections in Cirrhotic Patients with Gastrointestinal Bleeding: A Randomized Controlled Trial

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ABSTRACT

Background: According to the AASLD guidelines, fluoroquinolone and ceftriaxone are both recommended as antibiotics of choice for prophylaxis in cirrhotic patient with gastrointestinal bleeding (GIB). Limited studies exist comparing the efficacy of these two agents.

Objective: To compare the efficacy of intravenous ceftriaxone and ciprofloxacin for the prevention of bacterial infections in cirrhotic patients with GIB.

Methods: Overall 273 cirrhotic patients with GIB were enrolled between 2007 and 2010. Eighty four eligible patients were randomly assigned to receive either intravenous ceftriaxone or intravenous ciprofloxacin. All patients received intravenous octreotide and underwent esophagogastroduodenoscopy (EGD) with standard therapeutic approach. Blood cultures were routinely performed at initial, 2 hours post EGD, and at day 3. A 10-day infection rate, 10-day rebleeding rate, length of stay (LOS) and mortality during admission were recorded.

Results: Forty four cirrhotic patients with GIB were enrolled in each group. The baseline characteristics were not different between the groups. Suspected breakthrough infection rate within 10 days between ceftriaxone and ciprofloxacin groups was the same (22% and 22%). Gram-negative bacilli were isolated from followed up hemocultures in two patients in the ciprofloxacin-group. One patient was infected with extended spectrum beta-lactam (ESBL) organism and finally died. Rebleeding rate, LOS and mortality rates were similar in the two groups.

Conclusions: The efficacy of intravenous ceftriaxone and ciprofloxacin for the prevention of bacterial infection in cirrhotic patients with GIB is similar. The rates of breakthrough bacterial infections, rebleeding and mortality were not significantly different between two groups.

Key words : Prevention, ciprofloxacin, ceftriaxone, bacterial infection, cirrhotic, gastrointestinal bleeding

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Bacterial infections associated with gastrointestinal bleeding (GIB) are a very important and serious problem in cirrhotics[1-3]. Antibiotic prophylaxis can reduce infectious complications and also re-bleeding rate in cirrhotic patients with acute variceal bleeding compared to on demand antibiotics which are prescribed only when infection become evident[4-6]. Norfloxacin, an oral fluoroquinolone, is the pioneer antibiotic used to overwhelm the bacterial infections in cirrhotics with gastrointestinal hemorrhage and has become the most commonly used antibiotic prophylaxis in this condition[7,8]. However, the oral administration of antibiotics is not always possible in active gastrointestinal bleeding. Intravenous administration of fluoroquinolone; ciprofloxacin, has been shown to reduce the rate of infections by 35-40%[7-14]. Unfortunately, the prevalence of fluoroquinolone-resistant bacteria has increased substantially during the last years in many countries[15-19]. Third-generation cephalosporins seem to be an effective therapy in fluoroquinolone-resistant cirrhotic patients[4,6,19]. Intravenous ceftriaxone has been shown to be superior to oral norfloxacin in prophylaxis of spontaneous bacteremia and spontaneous bacterial peritonitis in advanced cirrhotic patients with GIB[6].

According to the AASLD guidelines 2007[5], short-term antibiotic prophylaxis should be given in cirrhotics with GIB. Ciprofloxacin and ceftriaxone are both recommended as antibiotics of choice. Ceftriaxone is preferred in an area with high prevalence of quinolones-resistant organisms. However, limited number of studies exists comparing the efficacy of these two agents for the prevention of bacterial infection in cirrhotic patients with GIB

The primary objective of this randomized controlled trial was to compare the efficacy of ceftriaxone and ciprofloxacin as a prophylaxis against infections in cirrhotic patients with GIB. The rates of breakthrough bacterial infections, re-bleeding and mortality were analyzed

Materials and methods

Patients

The study was performed in cirrhotic patients in King Chulalongkorn Memorial Hospital (KCMH) who presented with upper gastrointestinal hemorrhage between October 2007 and May 2010. Diagnosis of cirrhosis was based on clinical, laboratory, and ultrasonographic data. Inclusion criteria were as follows: age 18-80 years, hematemesis and/or melena and/or hematochezia within 5 days before presenting at the Emergency Room (ER). Exclusion criteria were as follows: treatment with antibiotics within 1 week before hemorrhage, previous history of allergy to cephalosporins or fluoroquinolones, HIV infection, pregnancy or lactation, and the presence of any of the following signs of infection at presentation: fever ≥ 37.8˚C, white cell count in blood > 15,000 mm^3, polymorphonuclear (PMN) cell count in ascitic fluid > 250 cells/mm^3, > 15 leukocytes/field in the fresh urine sediment or chest x-ray compatible with pneumonia.

The study protocol and consent forms were approved by the ethics committee of Chulalongkorn University. The patients or their relatives signed informed consent prior to participation.

Treatment

All patients received standard treatment for suspected variceal bleeding including intravenous octreotide and underwent esophagogastroduodenoscopy (EGD) within 24 hrs with endoscopic treatment if indicated. Standard laboratory measurements were: complete blood count (CBC), liver tests, renal function tests and urinary examination were done in the first day at presentation. Patients who turned out to have non-variceal bleeding, such as peptic ulcer or esophagitis, had their octreotide withdrawn and received proton-pump inhibitors. Blood transfusions were provided to maintain hemoglobin level at 8 mg/dL. Rebleeding was defined as new hematemesis or new melena occurring from 48 hrs to 10 days after inclusion.

Randomization and infection diagnosis

Patients who fulfilled the inclusion criteria and did not have any exclusion criteria were randomized into the 2 groups by using consecutively numbered envelopes for the treatment assignments. The box of two was used for randomization method. The patients or their relatives were informed and sign the consent form at ER. No one refused to participate in this study. After randomization, both antibiotics were initiated at the ER within the first 12 hours after presentation. They were randomly assigned to receive either intravenous ceftriaxone 1 gm daily for 3 days followed by oral cefdinir 200 mg twice daily for 4 days or intravenous

ciprofloxacin 400 mg twice daily for 3 days followed by oral ciprofloxacin 500 mg twice daily for 4 days, respectively. The total course of antibiotics was therefore 7 days in both groups.

Two bottles for blood cultures were obtained on arrival, another one at 2 hours post EGD, and the last bottle at day 3 in every patient to rule out bacteremia. 5 mL of blood were withdrawn for each hemoculture bottle. In our hospital, we use automated blood culture system called "VersaTrek". Breakthrough bacterial infection was suspected if the patient had body temperature more than 38.50 or one of the following signs; chill, abdominal pain, productive cough, dysurea or leukocytosis developing in hospital. Infection screen included measurements of white blood cell count in ascites and bacterial culture as well as blood and urine culture. The minimum amount of 10 mL of ascitic fluid was inoculated in one bottle for aerobic blood culture (VersaTrek) for automated system[20]. Confirmed bacterial infection was defined by positive blood or ascitic fluid or urine culture. If culture was positive, the treatment was given according to culture sensitivity. The method for susceptibility testing in this study was Disc diffusion test. Combination disk method was used to extended spectrum beta-lactamase (ESBL) confirmation. The percentage of confirmed infection, a 10-day re-bleeding rate and mortality were then analyzed.

Statistical analysis

The sample size was calculated on the basis of an expected success rate of ceftriaxone usage at 75% (data from previous study[5]) and 40% in the success rate of overall ciprofloxacin usage (data from Microbiology Unit, Chulalongkorn Hospital). Forty-two patients had to be included in each group to obtain a p-value <0.05 with an α error of 5% and a β error of 10%.

Values are expressed as mean ± SD. Continuous variables were compared by the Student's t test. Discontinuous variables were compared by the x^2 test. The log-rank test was used to compare the difference between the survival rate in ciprofloxacin and ceftriaxone group. The SPSS version 17.0 for windows was used for statistical analysis. Differences were considered significant at the level of 0.05.

RESULTS

From October 2007 to May 2010, 273 cirrhotic patients with GIB presented to our ER were recruited. 185 patients were excluded initially because of; current antibiotic use (N=140), pre-existing infection (N=42), and HIV infection (N=3). The eligible 88 patients were randomized into the 2 groups by the date of admission in the hospital. Of these, 44 patients were in the group receiving intravenous ciprofloxacin for 3

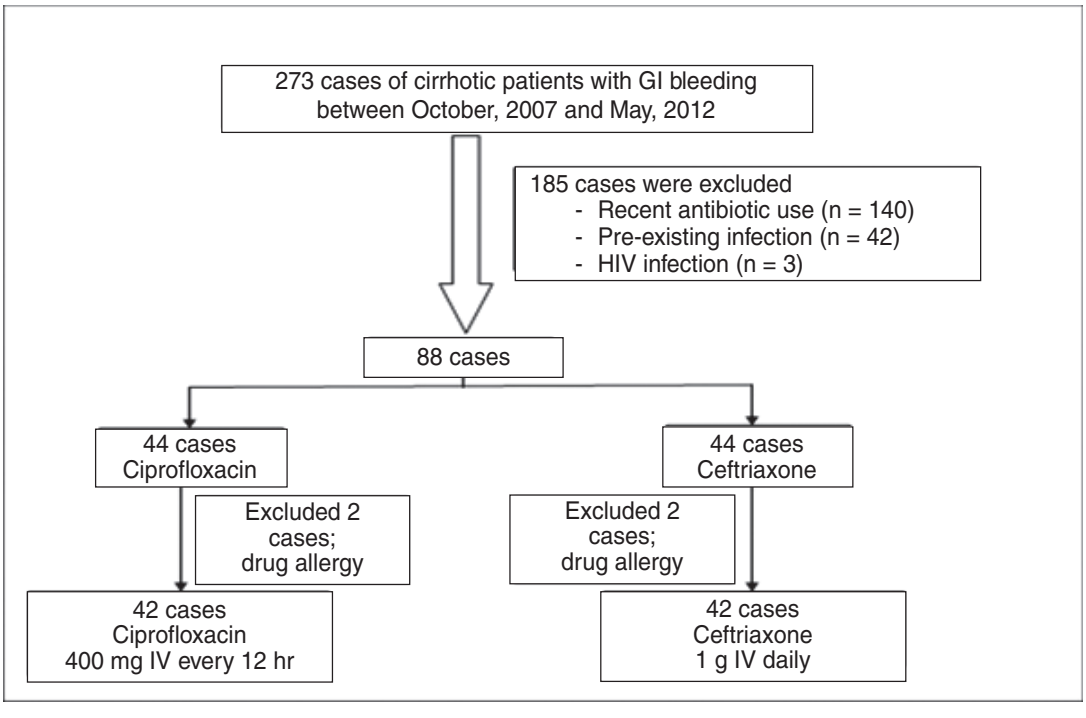

Figure 1. Flow diagram of patient allocation.

days and oral ciprofloxacin for 4 days. The other 44 patients received intravenous ceftriaxone and then cefdinir in the next 4 days. After randomization, the investigator needed to exclude 2 patients in each group due to antibiotics allergy. Thus, there are 42 patients left in each group (Figure 1).

For baseline characteristic, the mean age in our patients was 52±12 years. Most of them were males (79%) and the majority had alcoholic cirrhosis (41%). Forty percent of patients were Child-Pugh score A and the severity of cirrhosis was similar in the two groups. Variceal bleeding was the major cause of GI hemorrhage in our study at 56%. Forty-five percent of enrolled patients did not have any endoscopic treatment, whereas, for endoscopic intervention, band ligation was used predominantly in both groups (approximately 35%). All baselines characteristic were not different in the two groups (Table 1). Moreover, all patients had negative blood culture on arrival. In addition, the median bleeding interval before entry to the trial was 7 hours.

Bacterial breakthrough and outcomes

A total of twenty-two percent in each group had a suspected breakthrough bacterial infection (BT ≥38.5˚C) within 10 days. However, 2/42 (5%) of the ciprofloxacin group had gram-negative bacilli detected in hemocultures whereas no bacteremia occurred in ceftriaxone group. The isolated organism was *Escherichia coli* with negative extended spectrum beta-

Table 1. Baseline clinical characteristics.

Variables	Ciprofloxacin (n=42)	Ceftriaxone (n=42)	Total (n=84)	*p*-value
Age, mean ± SD (years)				0.58
	53 (10.7)	51 (13.8)	52 (12.3)	
Male, n (%)	29 (73)	34 (85)	63 (79)	
Etiology of cirrhosis, n (%)				0.08
- Alcohol	19 (45)	17 (41)	36 (41)	
- Hepatitis B	11(26)	5 (12)	16 (19)	
- Hepatitis C	3 (7)	5 (12)	8 (10)	
- Cryptogenic	4 (9.5)	1 (2.4)	5 (6.0)	
- NAFLD	0	1 (2.4)	1 (1.2)	
- Alcohol & HBV	1 (2.4)	8 (19.0)	9 (10.7)	
- Alchohol & HCV	3 (7.1)	5 (11.5)	8 (9.5)	
- Alcohol & HBV & HCV	1 (2.4)	0	1 (1.2)	
Child-Pugh score, n (%)				0.77
- A	16 (47.1)	18 (52.9)	34 (40.5)	
- B	14 (56)	11 (44)	25 (29.8)	
- C	12 (48)	13 (52)	25 (29.8)	
Cause of bleeding, n (%)				0.51
- Variceal bleeding	25 (59.8)	22 (52.5)	47 (56.0)	
- Peptic ulcer	8 (18.6)	10 (23.8)	18 (21.5)	
- Severe PHG	3 (7.2)	4 (9.5)	7 (8.3)	
- Mallory-Weiss-Tear	3 (7.2)	3 (7.1)	6 (7.1)	
- Others (Gastritis, esophagitis, tumor)	3 (7.2)	3 (7.1)	6 (7.1)	
Hemostasis methods, n (%)				0.633
- EVL	14 (33.3)	14 (33.3)	28 (33.3)	
- Glue injection	7 (16.7)	6 (14.3)	13 (15.5)	
- EVL& glue injection	2 (4.8)	1 (2.4)	3 (3.6)	
- APC	0	2 (4.8)	2 (2.4)	
- None	19 (45.2)	19 (45.2)	38 (45.2)	

lactamase (ESBL) on blood culture at the third day after presentation and this patient survived. The other patient had *Escherichia coli* with positive ESBL on the tenth day culture and died during the same admission. The 10-day rebleeding rate was 7.5% in the ciprofloxacin group and 5% in ceftriaxone group, respectively (NS). There was similar mean length of hospital stay in both groups which was approximately one week and equal death rate in both groups which was only 5%. Two patients in the ciprofloxacin group died from *Escherichia coli* septicemia with multi-drug resistant and intractable ruptured hepatoma, respectively. In the ceftriaxone group, both patients expired from severe septic syndrome with an unknown organism. In summary, the suspected breakthrough bacterial infection rate within 10 days, confirmed bacteremia, 10-day re-bleeding rate, death rate during admission and length of hospital stay between both groups were not significantly different between the ciprofloxacin and the ceftriaxone groups (Table 2).

DISCUSSION

To our knowledge, this is the first study of direct comparison of the efficacy between third-generation cephalosporins and fluoroquinolone for the prevention of bacterial infection in cirrhotic patients with GIB. The incidence of GIB in cirrhotic patients in King Chulalongkorn Memorial Hospital (KCMH) is approximately 90 patients per year (unpublished data). Clinically both ceftriaxone and ciprofloxacin have been used as a first choice of antibiotic prophylaxis for this condition. Even the prevalence of ciprofloxacin-resistant organisms in our hospital has increased to 40-60% in patients with gram negative bacilli infection (reported from Microbiology Unit, Chulalongkorn Hospital), we still had usually prescribed ciprofloxacin as an antibiotic prophylaxis for our patients presenting with GIB at the emergency room. The main reason for continuing ciprofloxacin treatment is that the outcome of treatment and mortality rate were not change even high rate of ciprofloxacin resistant. After exploring the data, we found that the prevalence of drug resistant in our hospital included both community and hospital acquired infection, whereas the present study evaluated mostly community acquired infection without history of recent antibiotic use. Therefore, our patients were low-risk of ciprofloxacin-resistant organism.

The important finding of our study is that the efficacy of both antibiotics was found to be similar. Nevertheless, the suspected bacterial infection rate was 22% which was higher than in previous studies (10-11%)[6,21] This difference might probably be explained by the definition of suspicious breakthrough bacterial infection in this study which was defined by high grade fever (BT ≥38.5˚C) "or" clinical suspicion of infection. However, confirmed infection rate was only 2.5%. This low percentage of proven infection may be due to no schedule of routine CBC, urinary examination and chest x-ray in this protocol. Moreover, the present study excluded patients with a history of recent 14-day antibiotic usage. Therefore, the patients with the high risk of drug resistant were not eligible for this study.

Both of proved infection in this study had *Escherichia coli* (*E.coli*) septicemia and they occurred in ciprofloxacin group. In our institute, the percentage of susceptible *E.coli* in ceftriaxone and ciprofloxacin was 52.38% and 40.69%, respectively (data from Microbiology Unit, Chulalongkorn Hospital, 2008). Therefore, patients in ciprofloxacin group may have a higher rate of E.coli infection. However, this difference is not significant in statistical analysis.

In addition, the mortality rate during the admission at 5% was lower than what has been reported in

Table 2. Outcomes of the study.

Variables	Ciprofloxacin (n=42)	Ceftriaxone (n=42)	Total (n=84)	*p*-value
Fever (BT≥38.5ºc) within 10 days	9 (22.0%)	9 (22.0%)	18 (22.5%)	0.60
Hemo/ascites/urine culture positive at day 3 or more during admission	2 (5%)	0 (0%)	2 (2.5%)	0.24
Rebleeding within 10 days	3 (7.5%)	2 (2.5%)	5 (6.25%)	0.48
Length of hospital stay (days, SD)	8.3±6.6	7.8±6.0	—	0.69
Death rate during hospitalization	2 (5.0%)	2 (5.0%)	4 (5.0%)	0.69

Table 3. Comparison data between this study and the previous studies.

	The current study	Fernández J, et al.[6] (Norflox vs. Cef-3)	Hsieh WJ, et al.[21] (Cipro vs. placebo)
Suspected breakthrough infection (%)	22	11	10
Confirmed infection (%)	2.5	11	10
Rebleeding rate (days)	<10	< 10	<7
Rebleeding rate (%)	6	9	6
Mortality rate (MR) during admission (%)	5	11	21
Decompensated cirrhosis (%)	60	100	90

previous studies. The lower mortality rate in our study may be explained by the lower proportion of patients with decompensated cirrhosis (60% vs. 90% from previous reports)[6,21] and some differences in the percentage of variceal bleeding (56% in this study vs. 68% in previous study)[6]. Confirmed breakthrough infection, 10-day re-bleeding rate and mortality rate were not different between the two groups in our study. Moreover, mortality in our study was from infection but the major cause of mortality in previous studies was liver failure (Table 3)[6,21].

Our study still has certain limitation. First, the numbers of case in this study were too small to provide the statistical power to conclude the indifferences of prophylaxis effect between these two agents. The success rate of overall ciprofloxacin usage in our hospital was at only 40% (data from Microbiology Unit, Chulalongkorn Hospital). This figure was calculated from every session of ciprofloxacin usage including hospital acquired infections. If the investigator could have the exact percentage of community acquired infections treated by ciprofloxacin, the success rate of ciprofloxacin treatment will be increased and the number of patients in the randomized control study should be more than 42 patients per arm.

Second, this study did not aim to determine the long-term follow up. However, the investigator calculated the 6-month mortality rate from the available data and found that the mortality rate was not significantly different between two medications (71% vs. 52%) with the high drop-out rate at 35%. Therefore, this long-term survival rate may not be representative for the total cohort. Surprisingly, the information on the 6-month mortality rate was not available in the previous studies[6,21].

From the last meta-analysis in 2011[22], it was confirmed that antibiotic prophylaxis in patients with cirrhotics and upper gastrointestinal hemorrhage will significantly reduce bacterial infections, all-cause mortality, rebleeding events and hospitalization length. However, bacterial resistance pattern has to be taken into consideration as this may vary by location, so antibiotic of choice should be assessed in the specific local settings. Focusing on our region, Sarin *et al.* provided the latest guideline of the Asian Pacific Association for Study of the Liver (APASL) which strongly recommended using short course of ceftriaxone 2-4 mg/day intravenously in cirrhotics with GIB[23].

The pattern of bacterial resistance is dynamic and changing over the time. For instance, in 1998, the combination of ceftriaxone and norfloxacin was not found to be of benefit in cirrhotics with GI bleeding[24]. Currently, fluoroquinolones are widely and easy to use in the community, so ceftriaxone is the recommended antibiotic for preventing the bacterial infection in the area of quinolones resistant. In the future, simple antibiotics should preferably be selected again as further studies maybe focus on the role of simple but targeted antibiotic to reduce the incidence of drug resistance. For instance, in a recent study, Xu *et al.* demonstrated a potential benefit of first generation cephalosporin (cefazolin), for prevention of bacterial infections in cirrhotic patients with acute variceal hemorrhage after endoscopic treatment[25]. The incidence of bacteremia was significantly lower in cefazolin usage compared with non-antibiotic administration and a trend of remaining free of early rebleeding within 7 days[25]. However, the incidence of gram negative bacilli resistant organism in their country was not mentioned.

CONCLUSION

The efficacy of intravenous ceftriaxone and ciprofloxacin for the prevention of community acquired

bacterial infection in cirrhotic patients with GIB is similar. The rates of breakthrough bacterial infection, rebleeding and mortality were not significantly different between the two groups. However, the appropriate antibiotic of choice should be assessed by the bacterial resistance pattern in that area.

Acknowledgements and conflict of interest

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