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Original Research Article

Comparison of intravenous ceftriaxone and ciprofloxacin in prevention of infection in cirrhosis patients with variceal bleeding

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ABSTRACT

Background: Patients with variceal gastrointestinal bleeding are very susceptible to bacterial infections. This study was designed to examine the effectiveness of ciprofloxacin and ceftriaxone in controlling in-hospital morbidity, mortality, and infection in variceal bleeding patients.
Methods: From August 2010 to August 2012, an interventional randomized controlled clinical trial was conducted in the Department of Gastroenterology, East Medical Ward, Mayo Hospital, Lahore. Adult patients who were diagnosed to have gastroesophageal variceal bleeding after endoscopic examination were included. These patients were randomly distributed to 2 groups. Group ceftriaxone: receiving injection Ceftriaxone 1000 mg intravenously 12 hourly for 7 days, Group ciprofloxacin: receiving injection ciprofloxacin 200 mg intravenously 12 hourly for 7 days.
Results: Most common viral etiology was Hepatitis C in both the study groups. It was observed that in the ceftriaxone group, 4.8% had rebleeding, while in the ciprofloxacin group 5.6% had rebleeding (p=0.77), one case each had porto-systemic encephalopathy (p=0.99), 0.8% in ceftriaxone group and 3.2% in ciprofloxacin group had spontaneous bacterial peritonitis (p=0.39) and 4.8% in ceftriaxone group and 8% in ciprofloxacin group had systemic inflammatory response syndrome (p=0.31). No patients died during one week follow up.
Conclusions: From our study, it was concluded that ciprofloxacin and ceftriaxone had same efficacy when used intravenously for prevention of bacterial infection and improvement in mortality and morbidity in patient of variceal bleeding. Future multicentric studies are required with a longer patient follow to support our findings.

Keywords: Variceal bleeding, Liver cirrhosis, Antibiotics, Infection, Sepsis

INTRODUCTION

Cirrhosis of the liver is the advanced stage of hepatic fibrosis; it is characterised histologically by the presence of regenerating nodules surrounded by severe fibrosis (scarring of the liver).[1] One-third of individuals with liver cirrhosis will exhibit no symptoms.[2] Anorexia, lethargy, weight loss, and muscle wasting are the most prevalent nonspecific and general signs among people with symptoms.

Cirrhosis of the liver raises resistance via the hepatic sinusoids, resulting in an increase in portal blood flow that causes endothelial dysfunction, an imbalance of vasodilator and vasoconstrictor factors, and a distortion of the hepatic vascular bed. Vasodilator factors and alterations in hepatic circulation result in arterial peripheric vasodilation, mostly in the splanchnic region, which leads to a hyperdynamic condition with reduced effective blood volume.[3] The presence of clinically significant portal hypertension (portal pressure gradient more than 10 mmHg) favours the development of collateral portosystemic circulation, portal hypertensive gastropathy, gastric varices, and oesophageal varices. The formation and progression of varices are dependent on the degree of portal hypertension and liver disease.[4] Kovalak

and colleagues found that 42 percent of patients with Child-Pugh class A and 71.9% of patients with Child-Pugh class B or C cirrhosis had varices.[5]

Variceal rupture, which is produced by high wall tension, results in variceal bleeding. Wall tension in oesophageal and gastroesophageal varices is influenced primarily by three variables: a rise in portal pressure, an increase in vessel size, and a reduction in wall thickness (Laplace's law). Therefore, the linked risk factors for developing variceal bleeding include portal pressure, vessel size, and endoscopic features of the vessel that translate to thinner vessel walls. (red marks).

Individuals with variceal gastrointestinal bleeding are very susceptible to bacterial infections. Up to fifty percent of active variceal bleeding episodes are associated with bacterial infections, and infections are regarded as an independent predictor of failure to control bleeding and death.[6] The most common infections are spontaneous bacterial peritonitis (SBP) and urinary tract infections, followed by pneumonia, skin and soft tissue infections, and bacteraemia. Cirrhosis patients with variceal haemorrhage are advised to take preventive oral or intravenous antibiotics, according to consensus recommendations.[7] Typically, intravenous cephalosporins (ceftriaxone 1 g every 24 hours for seven days) or oral quinolones are prescribed. (norfloxacin 400 mg every 12 hours for seven days). Also indicated are glycopeptides, aminoglycosides, macrolides, and rifaximin.[8] Very few studies have evaluated the clinical outcomes of liver cirrhosis patients with variceal haemorrhage who received intravenous ceftriaxone or ciprofloxacin. This research was designed to examine the effectiveness of ciprofloxacin and ceftriaxone in controlling in-hospital morbidity, mortality, and infection in variceal bleeding patients.

METHODS

Study design and sampling

From August 2010 to August 2012, an interventional randomized controlled clinical trial was conducted in the Department of Gastroenterology, East Medical Ward, Mayo Hospital, Lahore. Adult patients who were diagnosed to have gastroesophageal variceal bleeding after endoscopic examination were included. Patients who already had infection if clinically diagnosed, used antibiotic within 14 days, less than 18 years old, pregnant, had malignancy other than hepatocellular carcinoma, or were allergic to injection ceftriaxone and injection ciprofloxacin were excluded from the study. The sample size was 250 cases. The margin of error was 5% and confidence level was 95%. Each group ceftriaxone and ciprofloxacin contained 125 cases. The sample size n and margin of error E were given by:

$$x = Z(c/100)2r(100-r), N = N\,x/((N-1)E2 + x), E = Sqrt[(N-n)x/n(N-1)]$$

Where N is the population size, r is the fraction of responses that we are interested in, and Z (c/100) is the critical value for the confidence level c. Consecutive patients of variceal bleeding documented by endoscopic examination and without apparent evidence of infection were enrolled. Patient was randomized in two groups using random table. Informed written consent was obtained from all patients before enrolment in study.

Data collection and data analysis

Two hundred and fifty (250) patients fulfilling the inclusion and exclusion criteria admitted in East Medical Ward, Mayo Hospital Lahore were included in the study. After introduction and taking informed consent, history was taken from patient or close relative. The patients with upper gastrointestinal bleeding suggestive of cirrhosis of liver were admitted in accidents and emergency. After this proper history taking, general physical and systemic examinations were done, patients were randomized for intravenous antibiotics. These patients were randomly distributed to 2 groups. Group ceftriaxone: receiving injection Ceftriaxone 1000 mg intravenously 12 hourly for 7 days, Group ciprofloxacin: receiving injection ciprofloxacin 200 mg intravenously 12hrly for 7 days. Complete blood counts, platelet counts, liver function tests, prothrombin time, activated partial thromboplastin time, renal function tests with serum sodium and potassium, viral markers for hepatitis B and C, urinalysis, chest X-ray with a posteroanterior view, and ascitic fluid analysis for PMN cells, if present, were sent for laboratory evaluation. Standard treatment was given to all patients with upper gastrointestinal bleeding, including intravenous Octreotide, Lactulose, Colloid replacement, nasogastric lavage, and blood transfusions if necessary. As soon as the patients were stable, an esophago-gastroduodenoscopic (EGD) examination was conducted using an Olympus Exera II 180 endoscope, and endoscopic band ligation was performed. On the fourth day of hospitalization, prior to the administration of antibiotics to each patient, blood cultures were submitted following routine procedure. Patients with clinical suspicions of portosystemic encephalopathy and spontaneous bacterial peritonitis were submitted ascitic fluid examination for polymorphonuclear cells and culture, if available. The primary objective of the trial was to determine the pattern of mortality between the two study groups; additional outcomes included rebleeding, porto-systemic encephalopathy, spontaneous bacterial peritonitis, and systemic inflammatory syndrome.

Data were collected using a semi-structured study proforma, and analysed in SPSS version 23. The quantitative variables were described as means, while qualitative variables were described as frequency percentages. Means were compared using student's t test, while percentages were compared using chi-square test. A p value less than 0.05 was considered as statistically significant.

RESULTS

During the study period, we included 125 patients each in the group receiving ceftriaxone and ciprofloxacin, respectively.

It was observed that mean of the patients in the ceftriaxone and ciprofloxacin group was 51.54 and 50.21 years respectively, with no significant difference between them (p=0.41). In addition, 52.8% and 54.4% of the patients were males in the ceftriaxone group and ciprofloxacin group. Most common viral etiology was Hepatitis C in both the study groups (Table 1). It was observed that ascites was absent in 67.2% and 63.2% of the patients in the ceftriaxone and ciprofloxacin group respectively. Also, it was observed that in the ceftriaxone group, 92% had esophageal varices, 4.8% had gastric varices and 3.2% had both types of varices, and in the ciprofloxacin group, 92% had esophageal varices, 4% had gastric varices and 4% had both types of varices. Both the study groups were similar with respect to age, gender, viral etiology, severity of ascites and varices. Table 2 describes and compares mean values of various laboratory parameters and none of the laboratory investigations were found to be significantly different between ceftriaxone group and ciprofloxacin group. It was observed that in the ceftriaxone group, 4.8% had rebleeding, while in the ciprofloxacin group 5.6% had rebleeding (p=0.77), one case each had porto-systemic encephalopathy (p=0.99), 0.8% in ceftriaxone group and 3.2% in ciprofloxacin group had spontaneous bacterial peritonitis (p=0.39) and 4.8% in ceftriaxone group and 8% in ciprofloxacin group had systemic inflammatory response syndrome (p=0.31). No patients died during one week follow up.

Table 1: Baseline characteristics of the patients included in the study.

Variables	Group ceftriaxone (n=125) Frequency (%)	Group ciprofloxacin (n=125) Frequency (%)	P value
Mean age (years) ±SD	51.54±12.08	50.21±13.10	0.403*
Males	66 (52.8)	68 (54.4)	0.44**
Viral serology			
Hepatitis C	104 (83.2)	105 (84)	0.33**
Hepatitis B	5 (4)	1 (0.8)	
Both Hepatitis B and C	3 (2.4)	2 (1.6)	
None	13 (10.4)	17 (13.6)	
Severity of ascites			
Absent	84 (67.2)	79 (63.2)	0.77**
Mild-moderate	33 (26.4)	38 (30.4)	
Severe	8 (6.4)	8 (6.4)	
Varices			
Esophageal varices	115 (92)	115 (92)	0.91**
Gastric varices	6 (4.8)	5 (4)	
Both	4 (3.2)	5 (4)	

*analysed using Student's t test; **analysed using Chi-square test.

Table 2: Comparison of laboratory parameters between ceftriaxone and ciprofloxacin group.

Variables	Group ceftriaxone (n=125)	Group ciprofloxacin (n=125)	P value*
Haemoglobin (gm%)	9.31±2.43	8.71±2.69	0.069
TLC (x1000/cumm)	6.69±2.77	6.29±2.82	0.225
Prothrombin time (sec)	7.14±11.76	6.19±10.47	0.5
APTT	10.96±16.63	8.39±10.99	0.151
Platelet count (x1000/ml)	122.58±76.56	123.51±77.77	0.924
Total Bilirubin (mg/dl)	1.57±2.96	1.54±2.33	0.928
ALT (mg/dl)	73.88±65.65	81.03±90.38	0.475
AST (mg/dl)	86.18±67.45	98.23±132.99	0.367
Alkaline phosphate	277.07±135.58	277.81±157.62	0.968
Albumin (mg/dl)	3.60±0.56	3.43±0.54	0.019
Globulin (mg/dl)	2.78±0.62	2.77±0.63	0.848
Urea (mg/dl)	50.82±27.57	47.38±22.79	0.282
S. creatinine (mg/dl)	1.23±0.98	1.11±0.56	0.229
S. sodium (mEqdl)	135.45±4.02	136.03±3.28	0.209
S. potassium (mEq/dl)	3.89±0.44	3.86±0.49	0.61

*analysed using Student's t test.

Table 3: Comparison of various clinical endpoints between ceftriaxone and ciprofloxacin group.

Clinical endpoints		Group ceftriaxone (n=125) Frequency (%)	Group ciprofloxacin (n=125) Frequency (%)	P value*
Rebleeding	Yes	6 (4.8)	7 (5.6)	0.776
	No	119 (95.2)	118 (94.4)	
Porto-systemic encephalopathy	Yes	1 (0.8)	1 (0.8)	0.99
	No	124 (99.2)	124 (99.2)	
Spontaneous bacterial peritonitis	Yes	1 (0.8)	4 (3.2)	0.399
	No	124 (99.2)	121 (96.8)	
Systemic inflammatory response syndrome	Yes	6 (4.8)	10 (8)	0.301
	No	119 (95.2)	115 (92)	

*analysed using Chi-square test.

DISCUSSION

Since Rimola et al pioneering work showed that oral administration of nonabsorbable antibiotics significantly lowers the incidence of bacterial infections in cirrhotic patients with gastrointestinal bleeding, antibiotic prophylaxis is regarded the standard of treatment for these patients.[9] However, data from recent trials suggests that oral quinolone therapy may not be the optimal method for preventing bacterial infections in cirrhotic individuals with gastrointestinal haemorrhage. In recent years, the frequency of quinolone-resistant bacteria in the faecal flora, as well as the incidence of spontaneous bacterial peritonitis and other diseases caused by these organisms, have grown significantly.[10,11] However, a substantial proportion of infections in cirrhotic patients with gastrointestinal haemorrhage are caused by gramme-positive bacteria associated with the invasive procedures employed on these patients.

Since this class of antibiotics is effective against the majority of enterobacteria and aerobic gramme-negative bacilli, fluoroquinolones, including norfloxacin and ciprofloxacin, seem to be logical alternatives for prophylaxis. In a Taiwanese case-control study, 120 cirrhotic patients with upper GI bleeding who took ciprofloxacin 500 mg twice day after endoscopy for 7 days were shown to have a decreased incidence of proved bacterial infection (10% vs. 45%) but not death.[12] Patients with Child-Pugh Class C and hepatocellular carcinoma are highly susceptible to infection, and ciprofloxacin was proven to be extremely beneficial for these patients. In a research by Pauwels et al it was shown that 30 patients with advanced cirrhosis had a greater infection incidence than 55 patients with Child-Pugh Class A-B (52.9% vs 18.2%).[13] In the same study, a group of high-risk patients were given amoxicillin-clavulanic 1 g/200 mg iv q8h followed by ciprofloxacin 200 mg po q12h for 3 days after the cessation of bleeding, and a significant reduction in infection was observed compared to those who did not receive this regimen (13.3% vs. 52.9%). Tellez-Avila et al evaluated the effectiveness of ciprofloxacin for the primary prevention of bacterial infections in patients with liver cirrhosis and ascites.[14] 95 individuals were randomly assigned to the ciprofloxacin (N=49; 51.6%) or placebo (N=46; 48.4%) group. In the ciprofloxacin group, sixteen (32.6%) patients acquired bacterial infections, whereas thirteen (28.2%) patients in the placebo group developed bacterial infections. The chance of avoiding bacterial infections was not statistically significant (p=0.38). At 24 weeks, the probability of survival was 91% for the placebo group and 98% for the ciprofloxacin group (p=0.28).

There are rising reports of quinolone-resistant flora, particularly *Escherichia coli* and other gramme-positive infections, which may be connected to the invasive operations done on these individuals.[15] This led to a research from Barcelona in which 124 patients with severe cirrhosis were randomised into two groups (one group with 63 patients given oral norfloxacin 400 mg q12h for 7 days and the other group with 63 patients given iv ceftriaxone 1 g once daily for 7 days).[16] In the scientific literature, the length of antibiotic use ranges from 3 to 10 days.[17] A seven-day course of prophylaxis was more often prescribed and used.[18] In a study of infections in cirrhotic patients with upper gastrointestinal bleeding, conducted by Bernard et al the majority of infections occurred during the first five days after admission, and the majority of infections occurred within the first 48 hours.[19] The objective of Lee et al was to determine the duration of antibiotic treatment for cirrhotic individuals with acute esophageal variceal haemorrhage.[20] One group was administered 500 mg of intravenous ceftriaxone every 12 hours for three days, while the other group got the same regimen for seven days. There was no significant difference between the two groups in terms of rebleeding within 14 days (8% vs. 9%, p=0.99), transfusion quantity (2.71±2.84 units vs. 3.18±4.03 units, p=0.839), or survival rate in 28 days (100 vs. 97%, p=0.465).

A randomised controlled study was designed to examine the effectiveness of oral norfloxacin against intravenous ceftriaxone in preventing bacterial infection in cirrhotic individuals with gastrointestinal bleeding.[21] In their trial, 111 patients with advanced cirrhosis with gastrointestinal haemorrhage were randomly assigned to receive either oral norfloxacin (400 mg twice day; n=57) or intravenous ceftriaxone (1 g per day) for seven days. The trial's primary objective was to prevent bacterial infections within 10 days. The probability of developing proved or possible infections, proved infections, and spontaneous bacteremia or spontaneous bacterial peritonitis was significantly

increased in patients receiving norfloxacin (33% vs. 11%, p=0.003, 26% vs. 11%, p=0.03, and 12% vs. 2%, respectively; p=0.003, p=0.03, and p=0.03, respectively). There was no difference in hospital mortality between groups.[22]

Limitations

There are a few limitations of this study. This was a single centre study and thus the results of our study might not be generalizable to other geographic regions. Secondly, we could not perform long term follow up to assess the clinical outcomes of these patients.

CONCLUSION

From current study, it was concluded that ciprofloxacin and ceftriaxone had same efficacy when used intravenously for prevention of bacterial infection and improvement in mortality and morbidity in patient of variceal bleeding. Future multicentric studies are required with a longer patient follow to support our findings.

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