ORIGINAL Article

Norfloxacin 3 Days vs 7 Days in Cirrhotic Patients with Upper Gastrointestinal Hemorrhage : Infection Rate and Mortality, A Preliminary Report

*Ekawee Sripariwuth, M.D.**
*Duangporn Thong-ngam, M.D.***
*Rungsun Rerknimitr, M.D.**

ABSTRACT

Background: Bacterial infections are more frequent in cirrhotic patient who admitted with acute gastrointestinal hemorrhage compared with others. The incidences of infection reported in the world literatures were ranged from 14-67% with an overall incidence of 44%. The incidence of bacterial infection in cirrhotic patients in King Chulalongkorn Memorial Hospital was 30 % in 2001, usually occurred during the first three days of hospitalization.

Objective: To compare the effectiveness of a three-days course norfloxacin with a seven-days course to prevent bacterial infection during admission in cirrhotic patients with acute upper gastrointestinal hemorrhage.

Patients and Methods: From October 2002 until December 2003, all cirrhotic patients presented with acute upper gastrointestinal hemorrhage underwent gastroscopy within 24 hours and treated according to the endoscopic findings. During the first 24 hours of admission, blood, urine and ascitic fluid were sent for culture. After that, the patients were randomly allocated into two groups: group 1 received norfloxacin 400 mg twice a day for 3 days, group 2 received norfloxacin 400 mg twice a day for 7 days. All of them were observed for signs of bacterial infection during hospitalization and treated appropriately.

Results: Six patients (20.7%) from group 1 and none of the patients from group 2 developed infections. UTI and bacteremia were proved in two cases. All of the organisms isolated were gram-negative rods. The time of appearance of the infection was in the first three days of hospitalization. There was no mortality in both groups.

Conclusions: Three-days course norfloxacin 400 mg twice a day may be sufficient for prevention of bacterial infection in cirrhotic patients with acute upper gastrointestinal hemorrhage.

Key words : Norfloxacin, cirrhotic, upper gastrointestinal hemorrhage

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**Gastroenterology Unit, Department of Internal Medicine, **Department of Physiology, Chulalongkorn University, Bangkok 10330, Thailand.*

BACKGROUND

Cirrhotic patients have a high susceptibility to bacterial infection than normal host[1]. Three prospective series reported an incidence of infection in such patient ranging from 15-47%[2-4]. This incidence appeared to correlate with the severity of liver disease. Interestingly, bacterial infections are more frequent in cirrhotic patients who were admitted with acute gastrointestinal hemorrhage. The incidence of infection in these patients reported in the world literatures were ranged from 14-67% with an overall incidence of 44%[5-11]. According to recent studies, bacterial infections in cirrhotic patients with bleeding can be effectively prevented by antibiotic treatment. The preferred antibiotic was norfloxacin administered orally at a dose of 400 mg twice a day for 7 days[12]. However, in our anecdotal review in a small group of patients, bacterial infection usually occurred during the first three days of hospitalization. The aim of this study was to compare the effectiveness of a three-days course norfloxacin with a seven-days course to prevent bacterial infection during admission in cirrhotic patients with acute upper gastrointestinal hemorrhage.

PATIENTS AND METHODS

All cirrhotic patients presented with acute upper gastrointestinal hemorrhage at King Chulalongkorn Memorial Hospital between October 2002 and December 2003 were considered for inclusion in the study. The following patients were excluded : (a) patients with signs of infection at admission, (b) patients who were treated with antibiotics during the 1 week before admission, (c) patients who were allergic to quinolone, (d) pregnancy and lactation, and (e) patients who cannot receive oral medication. Careful physical examination, blood tests, urine, ascetic fluid and blood culture were performed during the first day of admission. All of these patients underwent gastroscopy within 24 hours and were treated according to the endoscopic findings. There were 54 cirrhotic patients fitted to our criteria. These patients were randomized into two groups; group 1 (n = 29) received norfloxacin, 400 mg twice a day orally for 3 days, and group 2 (n = 25) received norfloxacin, 400 mg twice a day orally for 7 days. The medication was started immediately after gastroscopy. All of them were observed for signs of bacterial infection during hospitalization. The whole period of the minimum length of stay was 7 days. The diagnostic procedures were performed whenever patients showed signs of infection and empirical antibiotics were started properly.

The diagnosis of spontaneous bacterial peritonitis was made when >250 neutrophils/μL were found in ascitic fluid positive culture results. The diagnosis of bacterascites was made at any instance of positive culture with ascitic fluid neutrophil count <250 neutrophils/μL. The diagnosis of bacteremia or urinary tract infection was made when the results of blood and urine culture, respectively, were positive and the clinical pictures were consistent with those diagnosis. Respiratory tract infection was diagnosed by clinical, bacteriological and radiological data. Patients who experienced fever and/or leukocytosis with a shift to the left and without any other evidence of infection were considered to have possible infections and were empirically treated with antibiotics as well.

Patients who died or underwent surgery within the first 24 hours after admission were excluded from analysis of results because the time elapsed was considered too short to allow for the action of norfloxacin.

Statistical analysis was performed by means of Student's t test and the chi-square test. A p value <0.05 was considered statistically significant. Continuous data were expressed as mean ± SD. The protocol was approved by the ethical committee of King Chulalongkorn Memorial Hospital. All patients gave informed consent before the study was begun.

RESULTS

There were no significant difference between both groups in the clinical and laboratory data of the patients on admission and during hospitalization (Table 1 and 2 respectively). Table 3 showed the features of the hemorrhage that were similar in both groups. There was no rebleeding during hospitalization.

The incidence and types of bacterial infections during the study period were shown (Table 4). Six patients (20.7%) from group 1 and none of the patients from group 2 developed infections. Infection (UTI) was proven in one patient and bacteremia developed in one patient. No septic shock was observed. The types of isolated organism were *E.coli* and *V.cholera non o-1*. There was no mortality at one week. The time elapsed between admission and the diagnosis of infection was 2.2 days (range, 1-3). We did not ob-

Table 1 Clinical characteristics of both groups of patients on admission

	Group 1 (n = 29)	Group 2 (n = 25)
Age (year)	49 ± 10	55 ± 12
Gender (Male/Female)	24/5	19/6
Etiology of cirrhosis		
Alcohol	18	16
Viral infection (HBV/HCV)	8	9
Other	4	3
Child Pughs'classification (A/B/C)	1/13/15	3/13/9
Encephalopathy	1	1
Total bilirubin (mg/dl)	4.4 ± 4.3	3.4 ± 3.8
Albumin (g/dl)	2.5 ± 5.2	2.7 ± 0.4
Prothrombin time (second prolonged)	5 ± 3.4	5 ± 6.6
BUN (mg/dl)	24.6 ± 13.5	26 ± 13.1
Creatinine (mg/dl)	0.9 ± 0.43	1.1 ± 0.5
Hematocrit (%)	25.4 ± 5.6	23.3 ± 5.7
White blood cell count (/μL)	8,848 ± 3,222	9,641 ± 5,798

Group 1: 3-days group
Group 2: 7-days group

Table 2 Clinical characteristics of patients during hospitalization

	Group 1 (n = 29)	Group 2 (n = 25)
Cause of bleeding EV/GV/PU/other	22/1/3/3	18/5/1/0
Hypovolemic shock	2	3
PRC (unit)	2.8 ± 1.6	2.8 ± 1.5
Endoscopic treatment		
EVL/Glue/Adrenaline injection	22/2/2/4	18/5/1/0
+ Electrocauterization/No Rx	11	14
Vasoactive drug	0	0
Surgery		
Day of infection (after admission)	1/3/2/0	0
1st / 2nd / 3 rd/ other	0	0
1-week mortality	0	6.4 ± 2.9
Length of stay (days)	7.3 ± 5.5	

Group 1: 3-days group
Group 2: 7-days group
EV = Esophageal varice, GV = Gastric varice, PU = Peptic ulcer, EVL = Esophageal varice ligation

serve any side effect from norfloxacin during the study period.

DISCUSSION

Cirrhotic patients with upper gastrointestinal hemorrhage were proned to bacterial infection. The incidence of bacterial infections was 20.7% and 0% in group 1 and group 2 respectively. Many reports showed that the incidence of the infection was 7-20% in the prophylactic groups[5-9]. Our result in the seven-days group was lower than the previous reports. It should be noted that, we did not perform blood culture daily after enrolling of the patients. Therefore, the true incidence of bacterial infection in these patients might be higher than the result of the present study indicated.

Table 3 Bacterial infections diagnosed in both groups

	Group 1 (n = 29)	Group 2 (n = 25)
Proved Infection	2	0
bacteremia	1	0
UTI	1	0
Possible Infection	4	0
Total	**6**	**0**

Group 1: 3-days group
Group 2 : 7-days group

Table 4 Bacteria responsible for infection

	Group 1 (n = 29)	Group 2 (n = 25)
Aerobic gram-negative bacilli	2	0
Escherichia coli	1	0
Vibrio cholera non o-1	1	0

Group 1: 3-days group
Group 2 : 7-days group

The time of appearance of infection was varied between 2-10 day after admission in the pervious studies[5-9]. Our results showed that all of the infections occurred within 72 hours of admission. Hsieh *et al*. also reported that half the patients in both groups developed infection within 48 hours after enrollment[9]. Pauwels *et al.* showed that almost all high risk patients (17/18, 94%) who did not received antibiotic developed infections during the first four days of hospitalization[8]. This suggested that the bacterial infections of bleeding cirrhotic patients were document shortly after the episode of hemorrhage. However, late infection could occurred in these patients too. Soriano et al found the incidence of late infection was 15% (4/26) in the prophylactic group (days 21-26 of hospitalization)[6]. This study followed the patients throughout hospitalization while the others followed the patients for 7-14 days or 10 days after cessation of the hemorrhage. However, in our study, we only observed the patients for the infection during the hospitalization. This will explained the difference between the time of appearance of infection in our report and the others.

Enteric gram-negative bacilli were bacteria most frequently responsible for infections in our patients.

Table 5 Development of infection in randomized- controlled trials of cirrhotic patient admitted with acute upper gastrointestinal hemorrhage

Author (year) Number of patient (prophylactic:control)	Antibiotic	Duration of antibiotic	Follow-up (time after admission)	Developed infection	Time of appearance of infection (after admission) Prophylactic : control
Rimola (1985)[5] 68:72	Genta/vanco/ nystatin or neomycin/colistin/ nystatin	From admission to 48 hours after cessation of hemorrhage	10 days after cessation of hemorrhage	11 (6%) : 25 (35%)	10.9 ± 3.8 : 10.1 ± 3.6
Soriano (1992)[6] 59:60	Oral norfloxacin	7 days	Throughout hospitalization	6 (10%) : 22 (37%)	4.5 ± 3.2 : 5.7 ± 7.6
Blaise (1994)[7] 45:46	Ofloxacin iv then oral	10 days	14 days	9 (20%) : 30 (60.7%)	5.8 ± 1.4 : 5.3 ± 2.1
Pauwels (1996)[8] 55:30	Amoxi/clavulanic + ciprofloxacin	From admission to 3 days after cessation of hemorrhage	10 days after cessation of hemorrhage	2 (7%) : 8 (14%)	8 ± 2 : 1.9 ± 0.2
Hsieh (1998)[9] 60:60	Oral ciprofloxacin	7 days	7 days	6 (10%): 27 (45%)	3.2 ± 2.0 : 2.3 ± 1.6
Ekawee (2004) 29:25	Oral norfloxacin	7 days/3 days	Throughout hospitalization	8 (20.7%) : 10 (30%)	2.2 : 0

Table 6 Mortality in randomized -controlled trials of cirrhotic patient admitted with acute upper gastrointestinal hemorrhage

Author (year)	In-hospital mortality prophylactic : control	Death from infection prophylactic : control
Rimola (1985)[5]	18 (27%) : 23 (32%)	1 (14%) : 7 (41%)
Soriano (1992)[6]	4 (7%) : 7 (12%)	NS
Blaise (1994)[7]	11 (24%) : 16 (35%)	0 : 2 (12%)
Pauwels (1996)[8]	4 (13%) : 8 (24%)	1 (25%) : 3 (38%)
Hsieh (1998)[10]	13(22%) : 18 (30%)	NS
Ekawee (2004)	0	0

NS: Not Stated

We did not find infection caused by gram-positive cocci. This suggested that the empirical antibiotic needed for bleeding cirrhotic patients who received selective intestinal decontamination should cover enteric gram-negative bacteria. Some authors found that gram-positive cocci frequently caused infections in patients undergoing selective intestinal decontamination such as norfloxacin and supported the use of antibiotics that covered these organisms when the infection was suspect in these patients[13-15].

In the previous studies, the mortality rate in cirrhotic patients with upper gastrointestinal hemorrhage who received antibiotic prophylaxis was ranged from 7-27%[5-9]. However, there was no mortality in our series.

Norfloxacin administered orally for three days was well-tolerated and convenient. There was no adverse effect. All of our patients received the medication completely during hospitalization.

In conclusion, three-days course norfloxacin 400 mg twice a day may be sufficient for prevention of bacterial infection in cirrhotic patients with acute upper gastrointestinal hemorrhage. A great number of samples were needed to assess the effectiveness of the three-days regimen.

REFERENCES

1. Wyke RJ. Problems of bacterial infection in patient with liver disease. Gut 1987; 28: 623-41.
2. Yoshida II, Hamada T, Inuzuka S, *et al*. Bacterial infection in cirrhosis, with and without hepatocellular carcinoma. Am J Gastroenterol 1993; 88: 2067-71.
3. Deschenes M, Villeneuve JP. Risk factors for the development of bacterial infections in hospitalized patients with cirrhosis. Am J Gastroenterol 1999; 94: 2193-7.
4. Caly WR, Strauss E. A prospective study of bacterial infection in patients with cirrhosis. J Hepatol 1993; 18: 353-8.
5. Rimola A, Bory F, Teres J, *et al*. Oral, nonabsorbable antibiotics prevent infection in cirrhotics with gastrointestinal hemorrhage. Hepatology 1985; 5: 463-7.
6. Soriano G, Guarnerr C, Tomas A, *et al*. Norfloxacin prevents bacterial infection in cirrhotics with gastrointestinal hemorrhage. Gastroenterology 1992; 103: 1267-72.
7. Blaise M, Pateron D, Trinchet JC, *et al*. Systemic antibiotic therapy prevents bacterial infection in cirrhotic patients with gastrointestinal hemorrhage. Hepatology 1994; 20(1 Pt 1): 34-8.
8. Pauwels A, Mostefa-Kara N, Debens B, *et al*. Systemic antibiotic prophylaxis after gastrointestinal hemorrhage in cirrhotic patients with a high risk of infection. Hepatology 1996 ; 24: 802-6.
9. Hsieh WJ, Lin HC, Hwang SJ, *et al*. The effect of ciprofloxacin in the prevention of bacterial infection in patients with cirrhosis after upper gastrointestinal bleeding. Am J Gastroenterol 1998; 93: 962-6.
10. Bernard B, Cadranel JF, Valla D, *et al*. Prognostic significance of bacterial infection in bleeding cirrhotic patients: a prospective study. Gastroenterology 1995; 108: 1828-34.
11. Goulis J, Armonis A, Patch D, *et al*. Bacterial infection is independently associated with failure to control bleeding in cirrhotic patients with gastrointestinal hemorrhage. Hepatology 1998; 27: 1207-12.
12. Rimola A, Garcia-Tsao G, Navasa M, *et al*. Diagnosis, treatment and prophylaxis of spontaneous bacterial peritonitis : a consensus document. J Hepatol 2000; 32: 142-53.
13. Gines P, Rimola A, Planas R, *et al*. Norfloxacin prevents spontaneous bacterial peritonitis recurrence in cirrhosis : results of a double-blind placebo-controlled trial. Hepatology 1990; 12: 716-24.
14. Soriano G, Guarner C, Teixido M, *et al*. Selective intestinal decontamination prevents spontaneous bacterial peritonitis. Gastroenterology 1991; 100: 477-81.
15. Tomas A, Soriano G, Guarner C, *et al*. Analisis de las infecciones bacterianas intrahospitalarias enpacientes cirroticos sometidos a descontaminacion intestinal selective. Rev Esp Enferm Digest 1991; 79: 259-64.