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Comparative Study Between Norfloxacin and Ciprofloxacin in Prophylaxis of Spontaneous Bacterial Peritonitis in Cirrhotic Patients

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ABSTRACT

This study was conduct prospective randomized study to compare efficacy of ciprofloxacin, 750 mg weekly, with norfloxacin, 400 mg daily, in prophylaxis of spontaneous bacterial peritonitis in cirrhotic patients. From March 2005 to Jan 2006, 25 patients were randomized by block of four to receive prophylaxis antibiotic with norfloxacin 400 mg daily (N group) or Ciprofloxacin 750 mg weekly (C group). Both groups will follow up as outpatients monthly for 6 months. There were no difference in baseline characteristic of both groups. Ascites fluid culture was positive 3/13 patients from norfloxacin group and 2/12 patients from ciprofloxacin group reported E.coli. Only 1/13 patient from ciprofloxacin group infected with Klebsiella pneumoniaei. No serious adverse reaction reported from both groups. We concluded that there were no differences prophylaxis between ciprofloxacin group and norfloxacin group.

Key words : SBP, peritonitis, ciprofloxacin, norfloxacin

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BACKGROUND

Cirrhosis is a frequent condition in internal medicine and likely to develop complications. Spontaneous bacterial an important complication in these patients. Hospitalized patients had spontaneous bacterial peritonitis range from 10-30%[1]. Mortality rate can be as high as 30% even early diagnosis and treatment is done[2]. Important risks for bacterial peritonitis are gastrointestinal bleeding, ascetic fluid protein less than 1.0 mg/dl and previous history of spontaneous bacterial peritonitis. Antibiotic prophylaxis in gastrointestinal hemorrhage patients has been shown to decreased infection rate[3,4]. Antibiotic prophylaxis in low ascitic protein (<1.0 mg/dl) is also decreased the risk for bacterial peritonitis when compared with placebo[6-9]. One year recurrent bacterial peritonitis is as high as 69% in patients who previously had bacterial peritonitis.[2] Antibiotic prophylaxis in these patients

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had the recurrent rate at 22% when compared with 68 % in the placebo group[10]. Moreover prophylaxis antibiotic is found to be more cost-effectiveness than treatment[11].

Prophylaxis antibiotic used in these studies was quinolone compound group which had action against gram negative bacilli. Gram negative bacilli are important pathogen in spontaneous bacterial peritonitis. A study compared between norfloxacin 400 mg per day with placebo. Recurrent rate in placebo group was 9% and no recurrent infection in norfloxacin group8. The main problem after prophylaxis antibiotic was bacterial resistance to drug used. Ciprofloxacin administration weekly also had decreased recurrent infection. Ciprofloxacin 750 mg weekly for 6 months had recurrent infection 4% compared with 22% in placebo group.[9] Interestingly, group which received ciprofloxacin weekly none was shown to had bacterial resistant to antibiotic used[9] while in study of norfloxacin as prophylaxis antibiotic found resistance organism may be as high as 69%[12].

Ciprofloxacin in role of antibiotic prophylaxis can be used as weekly dose can make convenient and can increase compliance for patients. And in past study did not found resistance strain to ciprofloxacin. So we conduct prospective randomized study to compare efficacy of ciprofloxacin, 750 mg weekly, with norfloxacin, 400 mg daily, in prophylaxis of spontaneous bacterial peritonitis.

Method and Material

Patients selection

Prospective randomized comparative trial in cirrhotic patient risk which have risk factor for spontaneous bacterial infection in Rajvithi hospital. High risk patients were patients who have previous history of spontaneous bacterial peritonitis (SBP) and/or who have ascetic protein less than 1.0 mg/dl. SBP was diagnose by ascitic PMN more than 250/mm^3 with clinical, laboratory and no radiologic evidence of secondary bacterial peritonitis or any abdominal pathology such tuberculosis, peritonitis, hemorrhage or carcinomatosis. Exclusion criteria was Renal failure (Serum creatinine >1.5 mg/dl), presence of hepatocellular carcinoma and drug allergy to quinolone group.

Treatment protocol

Patient was allocate to study group by block of four randomization to received prophylaxis antibiotic norfloxacin 400 mg daily (N group) or Ciprofloxacin 750 mg weekly (C group). Both groups will follow up as out-patients monthly for 6 months. Baseline characteristic (age. sex, etiology of cirrhosis, CPT score and complication of cirrhosis) was collect by the time of enrollment. Clinical and laboratory was collected at each visit and at the end of follow up. Patients who had gastrointestinal hemorrhage during follow up time will switch antibiotic to norfloxacin 400 mg twice daily or others appropriated antibiotic and switched to protocol drug when they was discharge from hospital. Any patient who had sign or symptom of infection will investigate further including abdominal paracentesis if they had suspected of SBP. Patients who had infection others than SBP will treat with appropriate antibiotic and switch to protocol drug after completed treatment. Those who had spontaneous bacterial peritonitis before end of follow up will be define as recurrence bacterial peritonitis. End point was those who had recurrence bacterial peritonitis. Those who died from other than SBP, who losses follow up and who cannot tolerate drug treatment will not include in this study.

Statistic analysis

Sample sized was calculated on basis of previous study that prophylaxis with norfloxacin had no infection and with ciprofloxacin had infection rate 9 % . On the basis of $\alpha = 0.05$, $\beta = 0.02$, Pc (norfloxacin group) = 0% and Pt (ciprofloxacin group) = 9%. A sample size was 66 per each group. However due to shortage of collective time. Sample groups in this study was not reached estimated sample sized. And data will be calculated as preliminary study. We used chi-square to compare between nominal parameter and t-test to compare numeric parameter. SPSS version 13 program was used to calculate all data.

Result

Due to limited time of studied, we collected data from only 25 patients that far from calculated 132 patients and made this study had less power to detect any significant between 2 experimental groups. Any way this studied may give a clue for further larger studied in the future. From March 2005 to Jan 2006 at Department of Internal medicine, 41 cirrhotic patients were screening to enroll in this study. There were 12 patients excluded from this study. 6 patients had renal

failure (serum creatinine >2.0 mg/dl), 3 patients had hepatocellular carinoma 2 patients had severe gastrointestinal bleeding and subsequently dead. And 1 patient had severe sepsis. In remaining 29 patients 4 cases was unable to follow up as study protocol. So only 25 patients was randomized to study. 13 patients were randomized to receive norfloxacin 400 mg daily and 12 patients were randomized to receive ciprofloxacin 750 mg weekly as prophylaxis antibiotic. And 10 baseline parameter define as age, sex, etiology of cirrhosis (viral or non viral), Gastrointestinal bleeding. Hepatic encephalopathy, serum total billirubin (mg/dl), Serum albumin (mg/dl), ascetic protein (mg/dl), Child-Pugh-Turcot score and positive ascetic fluid culture of both group was collected during time of enrollment. Baseline characteristic of both groups was not difference as show in Table 1

Ascitic fluid culture was positive in 6 patients. 3 patients from norfloxacin group have *E. coli*. 2 patient from ciprofloxacin group was also infected with *E. coli*. Only one patient from ciprofloxacin group infected with *Klebsiella pneumoniaei*. All of those organisms were sensitive to third generation cephalosporin given. About drug safety and adverse reaction to prophylaxis drug given. There are reports only minor adverse effects report from norfloxacin group 3 patients had nausea and 2 had headache. All of those were symptomatic treatment and symptom disappeared after follow up. There was no adverse reaction reported from ciprofloxacin group. No serious adverse reaction report from both groups.

Spontaneous bacterial peritonitis after prophylaxis antibiotic

There was 3 SBP and all of 3 infections occur in ciprofloxacin group (25 %, 3/12). 2 patient s had SBP at 3 months period which 1 patient occurred with hepatic encephalopathy and 1 patient infection occurred after gastrointestinal hemorrhage. One patient had SBP after follow up for 4 months period. No one in norfloxacin group has SBP (0 %, 0/13). When compare in 2 groups there were no significant in SBP event in 2 groups (p = 0.09). Organism culture from blood, urine or ascitic fluid from 3 infected patients was negative. So we don't have data whether organism resisted to prophylaxis antibiotic or not. All SBP patients were treated by third generation cephalosporin and have clinical response to cephalosporin drugs. In 3 SBP Patient there are only one who have low ascetic fluid protein with previous SBP while the others not.

DISCUSSION

In general practice secondary prophylaxis with daily norfloxacin was widely accepted[13]. Ciprofloxacin was also used as prophylaxis antibiotic and had good result in both daily[14] and weekly dose[9]. In this study there were 3 SBP in ciprofloxacin group and none in norfloxacin group. There are no differences between both groups. There was previous study using long acting quinolone rufloxacin compare with norfloxacin in preventing recurrent SBP[15]. Rufloxacin had more probability of having SBP at 3 months period than norfloxacin (9%versus 3%, p = 0.03) but not at 1 years (36 % versus 26 %, p = 0.16). Moreover in patients who receive rufloxacin 2 in 12 patients had recurrent peritonitis from quinolone-resistant bacterial (one *E. coli* and one *K. pneumoniae*). And rufloxacin had 7 Enterobacteriacae infections while norfloxacin group not. When compared only Enterobacteriacae

Table 1 Baseline characteristic of both treatment groups

	Norfloxacin	Ciprofloxacin	P value
Age	40.93 SD 3.49	42 SD 4.51	0.51
Sex (male)	38% (5/13)	67% (8/12)	0.31
Chr viral infection	77% (10/13)	75% (9/12)	0.67
GI bleeding	15% (2/13)	42% (5/12)	0.15
Hepatic encephalopathy	46% (6/13)	42% (5/12)	1
Total billirubin	2.56 SD 0.57	2.65 SD 0.15	0.54
Serum albumin	2.45 SD 0.29	2.45 SD 0.48	0.97
Ascitic protein	1.28 SD 0.28	1.275 SD 0.25	0.92
CPT	10.23 SD 1.48	10.67 SD 2.06	0.54
Positive ascitic fluid culture	23 % (3/13)	25 % (3/12)	1

strain, norfloxacin group had more efficacy in prevent recurrent SBP than ciprofloxacin (0% vs 22%,p = 0.01). From that study the authors concluded that rufloxacin was not alternative to norfloxacin in preventing of recurrent SBP[15]. However in our study didn't found any difference in recurrent SBP during 6 months follow up period. All recurrence in ours study was occurred within 4 month. Two third of infection occurred in 3 months. The reason for this may be small population groups in this study that gave less power to detect any significant. If larger population was study may be the result will be the same as previous study. In our study no organism was culture from recurrent SBP. So we can't evaluate whether organism resisted to prophylaxis quinolone compound or not. There was increase incidence of gram positive bacteria culture from SBP patients[16]. Recurrent SBP in our study may be cause by gram positive organism that not sensitive to quinolone compound used. From this data it would wiser not to used ciprofloxacin as prophylaxis antibiotic routinely until its benefit are clearified. Recent study was shown that medical prophylaxis of variceal bleeding by beta blocker reduced incidences of bacterial peritonitis[17]. May be combine both variceal bleeding prophylaxis and bacterial prophylaxis could have much impact to bacterial peritonitis.

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