Rifaximin plus norfloxacin versus norfloxacin alone in primary prophylaxis of spontaneous bacterial peritonitis in patients with variceal bleeding

Ahmed A. Ghafar[a], Salah Rozaik[a], Ahmed Akef[b]

[a]Department of Internal Medicine, Hepatology and Gastroentrology Unit, [b]Department of Clinical Pathology, Faculty of Medicine, Mansoura University, Mansoura, Egypt

Correspondence to Ahmed A. Ghafar, MD, Department of Internal Medicine, Hepatology and Gastrentrology Unit, Faculty of Medicine, Mansoura University, Mansoura, Egypt
Tel: 0201003958489 - 050/2738540;
e-mail: drahmedsaleh1981@gmail.com

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Background
Spontaneous bacterial peritonitis (SBP) is an infection of the ascitic fluid in the absence of other intra-abdominal sources. The risk is high in those with concomitant gastrointestinal bleeding, low ascitic fluid protein, or a previous attack of SBP. Norfloxacin is used widely in the primary prophylaxis of SBP but resistance usually develops where rifaximin was introduced.
Patients and methods
A total of 80 patients with advanced liver cirrhosis attending the Hemostasis Unit, Emergency Hospital, Mansoura University, with upper gastrointestinal bleeding were subjected to full history, clinical examination, laboratory assessment, and ascitic fluid analysis. The patients were divided into two groups: the first group received rifaximin plus norfloxacin and the second group received norfloxacin only and the two groups were followed up for 1 year.
Results
The study enrolled 80 patients, 51 men and 29 women with a mean age of 58.83 ±5.02 years for group 1 and 58.35±4.95 years for group 2. There were no statistically significant difference between the two groups as regards the clinical or laboratory characteristics except for the presence of focal lesions that was significantly present in group 2. A significant increase in the incidence of SBP in group 2 was present with P=0.014. The median time of developing SBP was significantly shorter in the second group.
Conclusion
The addition of rifaximin to norfloxacin decreased the incidence rates of SBP in patients with variceal bleeding with significant improvement in patient survival.

Keywords:
norfloxacin, rifaximin, spontaneous bacterial peritonitis

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Introduction

Spontaneous bacterial peritonitis (SBP) is a primary form of peritonitis where infection of the ascitic fluid occurs in the absence of other abdominal sources. It is a major complication of ascites and represents the end result in a series of events, starting with intestinal bacterial overgrowth and the translocation of bacteria resulting in bacteremia, endotoxemia, colonization of mesenteric lymph nodes, and finally migration of bacteria into the ascitic fluid [1].

The prevalence of SBP is between 10 and 30% in cirrhotic patients with ascites. The risk is higher in those with a previous attack of SBP, low protein concentration in ascitic fluid, or presence of concomitant gastrointestinal (GI) bleed [2]. The endogenous microbial flora translocation into the blood stream usually occurs during any endoscopic procedure [3]. After diagnostic upper GI endoscopy, the mean frequency of bacteremia is about 4.2%. The rate can be more with therapeutic procedures [4].

The diagnosis of SBP is based on the presence of an elevated ascitic polymorphonucleocytes (PMNs) count (>250/mm). If the aspiration brings bloody fluid (>10 000 red blood cells/mm), then we should subtract one PMN for every 250 red blood cells to determine the ascitic PMN count. However, culture of the ascitic fluid is negative in 40% of cases of SBP diagnosed by elevated ascitic PMNs [5].

The main causes of death in patients with SBP are hepatorenal syndrome, sepsis, and liver cell failure. In addition, patients with SBP show poor prognosis where 1-year mortality is about 50–70% [6].

The high mortality rates of patients with SBP warrant the importance of its prevention. The aim of

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administration of antibiotics is to decrease the burden of bacteria in the gut, thus interrupting the sequence of events leading to ascitic fluid infection [7].

Norfloxacin at a dose of 400 mg daily is being used widely in the primary prophylaxis of SBP; however, its extensive long-term use leads to increased incidence of Gram-positive and quinolone-resistant SBP [7].

Rifaximin has a broad spectrum of antibacterial activity with high concentrations in stool and negligible absorption into the systemic circulation [8]. Therefore, it has been proposed as an oral candidate antibiotic to prevent SBP in the absence of systemic side effects [9]. Studies suggest that rifaximin suppresses intestinal bacterial overgrowth, which in turn reduces bacterial translocation, which may reduce the incidence of SBP in patients with liver cirrhosis [10,11].

Aim

In this study, we tried to assess the safety and efficacy of rifaximin plus norfloxacin in comparison to norfloxacin alone in primary prophylaxis of SBP in patients with variceal bleeding and its impact on patient survival.

Patients and methods

Patients

This is a comparative, descriptive, cross-sectional study that was conducted on 80 patients attending the Hemostasis Unit, Emergency Hospital, Mansoura University, from December 2016 to June 2018 with upper GI bleeding.

Inclusion criteria

(1) Patients aged 18–70 years of both sex.
(2) Patients with variceal bleeding either esophageal or gastric varices underlying the endoscopic therapy.
(3) Patients with decompensated liver cirrhosis (Child–Pugh B or C).
(4) No history of previous attacks of SBP.

Exclusion criteria

(1) Patients with non-variceal bleeding.
(2) Patients with compensated liver cirrhosis (Child–Pugh A).
(3) History of previous attacks of SBP.
(4) History of attacks of upper GI bleeding in the previous month.
(5) History of antibiotic use in the previous 2 weeks.
(6) History of GI surgery.
(7) History of previous *Helicobacter pylori* infection or treatment.
(8) Patients with renal impairment (serum creatinine >2 mg/dl).

All patients were subjected to full history taking with stress on history of previous attacks of upper GI bleeding, SBP, GI surgery, or history of previous attacks of hepatic encephalopathy. Complete examination with stress on manifestations of hepatic decompensation was done for all patients.

Laboratory assessment

Complete blood count, serum creatinine, complete liver function tests, hepatitis C virus antibodies, hepatitis B virus surface antigen, and complete ascitic fluid analysis were done for all patients.

Imaging studies

Abdominal ultrasonography was done for all patients to confirm the presence of ascites and aspiration of ascitic fluid sample.

The patients were divided into two groups:

(1) Group 1: patients who received rifaximin 550 mg twice daily plus norfloxacin 400 mg twice daily starting from the second day of bleeding.
(2) Group 2: patients who received norfloxacin 400 mg twice daily alone starting from the second day of bleeding.

The two groups were followed up for 1 year and examined every 3 months for ascitic fluid analysis or when clinical manifestations of SBP such as fever, abdominal pain, or tenderness are present. Diagnosis of SBP is confirmed when the ascitic fluid PMN count is more than 250/mm. The cause of death and the overall survival of patients were monitored. Drugs were stopped if an attack of SBP occurred (PMN count >250 cell/mm in ascitic fluid with or without clinical manifestations), had upper GI bleeding, or underwent liver transplantation.

Statistical analysis

Data were entered into a computer and analyzed using IBM SPSS software package version 20.0 (USA). Qualitative data were described using number and percentage. Quantitative data were described using mean, SD for parametric data after testing normality using the Kolmogrov–Smirnov test. Significance of the obtained results was judged at the 5% level and all tests were two-tailed.

Student's *t*-test and Mann–Whitney *U*-test were used to compare between two studied groups with

parametric and nonparametric variables, respectively. χ^2-test, Monte Carlo test and Fischer's exact test were used to compare categorical variables as appropriate. Kaplan–Meier survival curve and log-rank test were used to compare the effect of drug regimen use on SBP. Binary stepwise logistic regression analysis was used for the prediction of independent variables of SBP. Significant predictors in the univariate analysis were entered into the regression model using the forward Wald method. Relative risk and their 95% confidence interval were calculated.

Ethics

Written consents from the patients participated in the study or from their families were obtained and approved by the Mansoura Medical Ethics Committee (MMEC) of the Faculty of Medicine.

Results

The study enrolled 80 patients, 51 men and 29 women with a mean age of 58.83±5.02 years for group 1 and 58.35±4.95 years for group 2 (Table 1). In Table 2, we collect the clinical characteristics of the studied groups where there were no statistically significant difference between the two groups except for the presence of focal lesions that was significantly present in group 2. There were no statistically significant difference between the two groups as regards the laboratory characteristics as shown in Table 3.

Table 4 shows the incidence of SBP and cause of death in the two groups where a significant increase in the incidence of SBP in group 2 was present with P=0.014. Also, SBP and sepsis were significantly present as the main causes of death more in group 2 with P=0.01. Table 5 shows the median time of developing SBP in the studied groups where it was significantly shorter in the second group. Kaplan–Meier survival curve was used for drugs to predict survival among the studied groups as shown in Fig. 1. Table 6 shows the regression analysis in the prediction of SBP.

Table 1 Demographic characteristics of the studied groups

	Group 1 (combined norfloxacin and rifaximin) (N=40)	Group 2 (norfloxacin alone) (N=40)	Test of significance
Age (mean±SD) (years)	58.83±5.02	58.35±4.95	t=0.43 P=0.67
Sex [n (%)]			
Male	25 (62.5)	26 (65.0)	χ^2=0.05 P=0.82
Female	15 (37.5)	14 (35.0)	

Table 2 Clinical characteristics of the studied groups

	Group 1 (combined norfloxacin and rifaximin) (N=40) [n (%)]	Group 2 (norfloxacin alone) (N=40) [n (%)]	Test of significance
DM	17 (42.5)	15 (37.5)	χ^2=0.21 P=0.65
Hypertension	12 (30.0)	8 (20.0)	χ^2=1.07 P=0.30
Etiology of cirrhosis			
HCV	37 (92.5)	37 (92.5)	FET P=1.0
Bilharziasis	3 (7.5)	3 (7.5)	
Encephalopathy	17 (42.5)	22 (55.0)	χ^2=1.25 P=0.26
Focal lesion	12 (30.0)	26 (65.0)	χ^2=9.83 P=0.002*
Spleen			
Absent	6 (15)	2 (5.0)	MC P=0.22
Mild	12 (30.0)	15 (37.5)	
Moderate	20 (50.0)	21 (52.5)	
Marked	2 (5.0)	2 (5.0)	
Varices			
Band ligation	14 (35.0)	16 (40.0)	MC P=0.24
Sclerotherapy	22 (55.0)	21 (52.5)	
Cyanoacrylate	4 (10.0)	3 (7.5)	
Survival			
>1 year	22 (55.0)	11 (27.5)	MC P=0.04*
3 months	3 (7.5)	10 (25.0)	
6 months	7 (17.5)	11 (27.5)	
9 months	8 (20.0)	8 (20.0)	

DM, diabetes mellitus; FET, Fischer's exact test; HCV, hepatitis C virus; MC, Monte Carlo test. *P<0.05, statistically significant.

Table 3 Laboratory characteristics of the studied groups

	Group 1 (combined norfloxacin and rifaximin) (*N*=40) (mean±SD)	Group 2 (norfloxacin alone) (*N*=40) (mean±SD)	Test of significance
Albumin (g/dl)	3.025±0.38	2.88±0.39	*t*=1.6 *P*=0.11
WBCs	4.77±1.9	4.86±1.87	*t*=0.21 *P*=0.84
Hemoglobin (g/dl)	11.28±1.63	11.31±1.74	*t*=0.09 *P*=0.92
Platelet	100.38±43.2	103.85±48.7	*t*=0.34 *P*=0.74
INR	1.35±0.20	1.35±0.19	*t*=0.05 *P*=0.96
Ascitic fluid protein (g/dl)	1.43±0.26	1.39±0.16	*t*=0.04 *P*=0.88
ALT [median (minimum–maximum)]	34.0 (20.0–182.0)	34.0 (20.0–182.0)	*Z*=0.23 *P*=0.82
AST [median (minimum–maximum)]	67.5 (32.0–203.0)	68.5 (32.0–203.0)	*Z*=0.19 *P*=0.85
Bilirubin (mg/dl)	1.32 (0.60–24.0)	1.55 (0.80–3.5)	*Z*=0.18 *P*=0.86

ALT, alanine aminotransferase; AST, aspartate aminotransferase; INR, international normalized ratio; WBC, white blood cells.

Table 4 Incidence of spontaneous bacterial peritonitis and cause of death of the studied groups

	Group 1 (combined norfloxacin and rifaximin) (*N*=40)	Group 2 (norfloxacin alone) (*N*=40)	Test of significance
Spontaneous bacterial peritonitis	13 (32.5)	24 (60.0)	χ^2=6.08 *P*=0.014*
Cause of death			
Sepsis	3 (11.5)	9 (34.6)	MC *P*=0.01*
SBP	3 (11.5)	7 (26.9)	
Liver failure	7 (26.9)	7 (26.9)	
GIT bleeding	13 (50.0)	3 (11.5)	

GIT, gastrointestinal tract; MC, Monte Carlo test; SBP, spontaneous bacterial peritonitis. *$P<0.05$, statistically significant.

Table 5 Median time of developing spontaneous bacterial peritonitis between the studied groups

	Group 1 (combined norfloxacin and rifaximin) (*N*=40)	Group 2 (norfloxacin alone) (*N*=40)	Test of significance
Median survival time (weeks)	25.0 (1.0–25.0)	16.0 (1.0–25.0)	Log-rank χ^2=5.3 *P*=0.02*

Discussion

SBP is a major complication of ascites that affect a considerable number of patients with high morbidity and mortaliy. Primary prophylaxis of SBP have been associated with significant improvement in patient survival. Several studies have evaluated many protocols in the era of primary prophylaxis [12–14].

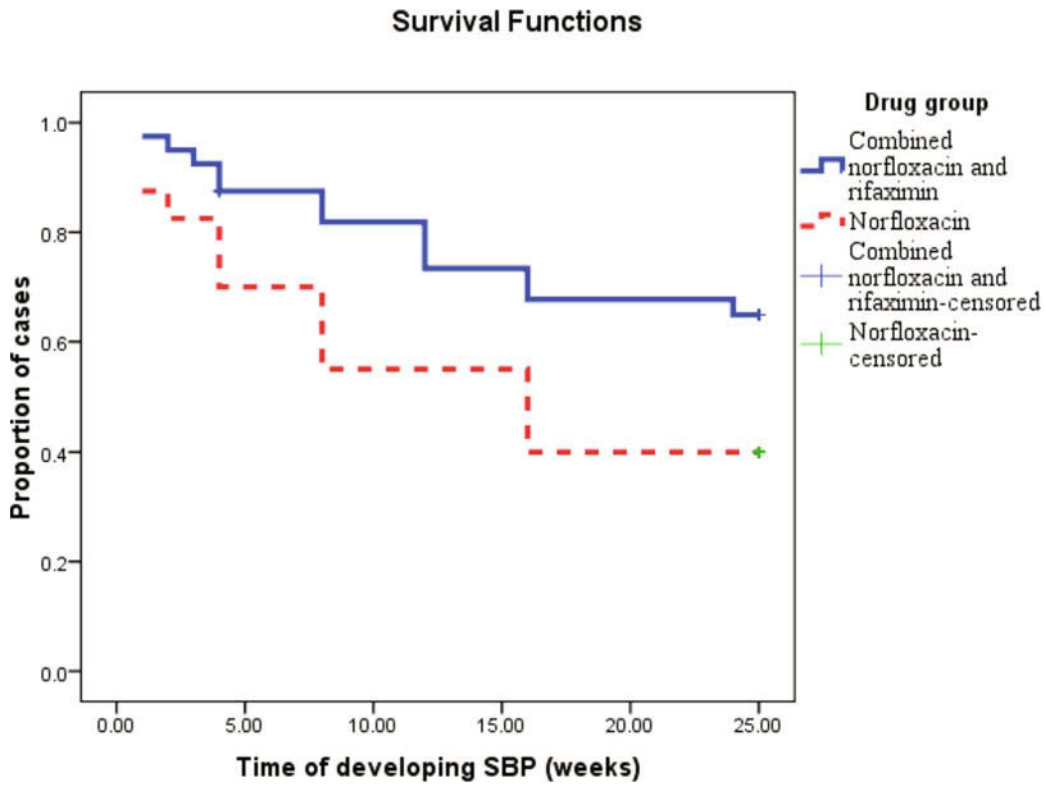
The risk of SBP increases in patients with GI bleeding and after diagnostic or therapeutic upper GI endoscopy as they are the main source of bacteremia and endotoxemia through translocation of bacteria from the gut to the ascitic fluid. Owing to the broad spectrum antibacterial effect of rifaximin in the gut with minimal systemic absorption, we evaluated the benefits of adding rifaximin to norfloxacin as a protocol for primary prophylaxis of SBP in patients with variceal bleeding.

In our study, we enrolled 40 patients in each group with a mean age of 58.83±5.02 years for group 1 and 58.35 ±4.95 years for group 2 with no difference in sex distribution between the two groups and this suggests that the two groups are cross-matched (Table 1).

In our study, we have included patients with high risk to develop SBP, so we enrolled patients with variceal bleeding as it is an important source of endotoxaemia even after diagnostic or therapeutic upper GI endoscopy [4]. We also enrolled patients with Child–Pugh class B and C which are indicative of the presence of advanced liver disease where low serum albumin and elevated serum bilirubin are predictors of SBP [15,16].

In the current study, when we analyzed the clinical and laboratory characteristics of our patients, we found no statistically significant difference between the two groups except for the presence of focal lesions that was significantly present in group 2 (Tables 2, 3). Also, there were no significant differences between the two groups as regards the presence of low levels of protein in the ascitic fluid which is a standarized risk factor for SBP especially in patients with GI hemorrhage (Table 3). This shows that the patients of the two groups are crossmatched as regards the degree of

Figure 1



Kaplan–Meier survival curve for drugs used to predict survival among the studied groups.

Table 6 Regression in the prediction of spontaneous bacterial peritonitis

		P	RR (95%CI)	ARR	NNT
Drug					
Combined (*r*) Norfloxacin	1.14	0.015*	3.12 (1.25–7.78)	0.275	3.64

ARR, absolute relative risk; CI, confidence interval; NNT, number needed to treat; *r*, reference group; RR, relative risk. *Statistically significant.

severity of liver disease and consequently the incidence rates of SBP in the two groups is related to the drugs used in primary prophlaxis.

To our knowledge, the combined use of norfloxacin and rifaximin as a protocol for primary prevention of SBP in high-risk patients has not been studied before, especially in Egypt where the majority of studies evaluated rifaximin or norfloxacin alone or their alternating use. Owing to the decreased efficacy of some prophylactic protocols based on norfloxacin, we evaluated the safety and efficacy of combined use of norfloxacin and rifaximin in the primary prevention of SBP in patients with variceal beeding.

In our study, the addition of rifaximin to norfloxacin showed considerable improvement in the primary prevention of SBP in comparison to norfloxacin alone, where 24 (60.0%) patients of group 2 developed SBP to 13 (32.5%) patients in group 1 with *P*=0.014 (Table 4) over the duration of follow-up. The higher incidence of SBP in patients with variceal bleeding who received norfloxacin alone may be partly explained by the recent advances in understanding the pathogenic microbiota responsible for SBP. Selective intestinal decontamination, using norfloxacin, may have led to the emergence of antibiotic-resistant microorganisms in the gut flora, which may be accused for the recent increase in the incidence of SBP caused by Gram-positive organisms [17,18]. However, in our study we have not isolated the bacteria causing SBP. Despite this, the higher efficacy of the combined use of norfloxacin and rifaximin in primary prophylaxis for SBP may be due to the broader spectrum coverage of rifaximin including Gram-positive organisms.

Fenandez *et al.* [19] evaluated norfloxacin use in primary prophylaxis which showed a 93% reduction in the incidence of SBP over 1 year when compared with placebo in comparison to our study that showed only 40% reduction in our patients who received norfloxacin. This discrepancy may be related to the scope of patients included in our study who show a high

risk to develop SBP besides the sporadic use of antibiotics in our community.

Prophylaxis of SBP with norfloxacin becomes not effective as in the past due to the increased frequency of bacteria resistant to quinolones in the fecal flora of patients with liver cirrhosis secondary to the widespread use of these agents [20]. Parallel to our study, Hanouneh *et al.* [21] showed 72% prevention rates of SBP in their study on 404 patients with cirrhotic ascites.

On the basis of these results, an important question arises which is about the percentage of patients in group 1 who developed SBP that represents 32.5% of cases (Table 4). This can be explained by a study in patients with liver cirrhosis demonstrating that treatment with rifaximin changed the pattern of metabolites, produced by the intestinal bacteria rather than the quantity of bacteria [22]. Another possible explanation for the occurrence of SBP under treatment with rifaximin is that direct bacterial translocation from the intestine may not be the only route of infection, as supported by the analysis of bacterial DNA in ascites [23].

In our study, we did not find any significant effect of the type of varices or the therapy applied to it on the incidence rates of SBP in our groups (Table 2). A meta-analysis showed a significant beneficial effect of prophylaxis with antibiotics in decreasing the occurrence of bacterial infections and mortality in patients with cirrhosis who develop GI bleeding where most of their groups were submitted to endoscopic therapies [3]. Patients with active or recent bleeding are more susceptible to the invasion of bacteria through a defective variceal wall [24].

In the present study, the median time of developing SBP was significantly prolonged in group 1 (25 weeks) in comparison to group 2 (16 weeks) with P=0.02 (Table 5 and Fig. 1). This was associated with a significant improvement in patient survival, where it was significantly prolonged in group 1 in comparison to group 2 with P=0.04 (Table 2). The mortality rates were higher in the second group and was related mainly to sepsis with P=0.01(Table 4).

In accordance with our study, Shamseya and Madkour [13] showed a reduction in mortality rate from 9.3% with norfloxacin compared with 7% with rifaximin. Similarly, Assem *et al.* [14] showed a reduction in mortality rate with rifaximin (2.4%) versus norfloxacin (7.6%). The leading causes of mortality across all studies were hepatic encephalopathy, sepsis, variceal bleeding, and hepatorenal syndrome. This demonstrates the beneficial effect of rifaximin on those patients. On the other hand, Frazee *et al.* [25]) concluded that cirrhotic patients with low ascitic fluid protein levels who has no previous SBP may benefit from long-term antimicrobial prophylaxis. However, the magnitude of the benefits was smaller and the incidence of overall infections and mortality are not changed [14].

The high cost of rifaximin may limit its use. The risk/benefits of rifaximin plus lactulose use for hepatic encephalopathy besides norfloxacin for prophylaxis of SBP compared with rifaximin plus lactulose alone may be of clinical interest especially in patients with GI bleeding. However, analysis of our data showed that the patients using norfloxacin alone is at an increased risk of SBP 3.12 times more than patients using a combined drug regimen; the clinician will need to treat four patients in order to prevent one SBP (Table 6).

Our study may be limited by some factors such as the relatively small number of patients included in the study, the etiology of liver disease, the effect of presence of hepatic focal lesions, time of starting prophylaxis, dose of drugs used, and lastly the lack of separation of microorganism causing SBP which prevents the sensitivity testing of the used antibiotics. Despite this, the results of our study showed that the addition of rifaximin to norfloxacin has a beneficial effect on the incidence rates of SBP as well as on the survival of patients with variceal bleeding; so our protocol may be suitable for this sector of patients.

Conclusion

Combined use of rifaximin and norfloxacin is superior to norfloxacin alone in primary prophylaxis of SBP in patients with variceal bleeding.

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Conflicts of interest

There are no conflicts of interest.

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