ORIGINAL ARTICLE

Norfloxacin versus rifaximin for spontaneous bacterial peritonitis prophylaxis: A randomized controlled trial

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Abstract

Background: Spontaneous Bacterial Peritonitis (SBP) is a bacterial infection of ascitic fluid occurring in patients suffering from cirrhosis and ascites exhibiting high short-term mortality rate and poor long-term prognosis. *Aim and Objectives:* Diagnosis based on ascitic fluid polymorphonuclear neutrophil count and culture was carried out. Norfloxacin is the current first-line prophylactic antibiotic treatment for SBP. The study aimed to compare the efficacy of norfloxacin and rifaximin in preventing SBP in patients with cirrhosis and ascites. *Material and Methods:* Total 66 patients were included, with 33 patients in each group. Patients in first group were administered 400 mg norfloxacin twice daily per orally, while other group was administered rifaximin 400 mg twice daily per orally for 3 months. The patients were followed up every month for three months to evaluate the signs and symptoms of SBP and other complications related to cirrhosis. *Results:* Mean age of all patients was 48.48 ± 10.44 years with majority being male. The most reported symptoms were decreased appetite and generalized weakness, while the most common sign detected was abdominal distention. Alcoholic liver disease was the most common etiology among patients with SBP. Hematological and biochemical parameters differed less significantly between two treatment groups, except for international normalized ratio values. At first, second and third follow-ups, more patients from norfloxacin administered group reported hepatic encephalopathy, gastrointestinal bleed, hepatorenal syndrome and SBP episodes than from rifaximin administered group. *Conclusion:* Overall, the study highlights effectiveness of rifaximin over norfloxacin in reducing the risk of complications in cirrhosis patients with ascites and Child Pugh Score > 9.

Keywords: Spontaneous Bacterial Peritonitis, Norfloxacin, Rifaximin, Hepatic Encephalopathy

Introduction

Gastro-intestinal tract related diseases are encountered more than other human body systems [1]. Spontaneous Bacterial Peritonitis (SBP) is a bacterial infection of the ascitic fluid arising without a definitive intra-abdominal surgically treatable source of infection. SBP is more common in patients with cirrhosis and ascites, with reported short-term mortality rates ranging from 10% to 50%. Furthermore, patients with SBP possess a poor prognosis, with 1-year mortality rate of 31–93% [2-3].

The clinical presentation of SBP varies from abdominal pain, tenderness, vomiting, diarrhoea, or ileus as common symptoms and/or signs. Additionally, signs of systemic inflammation such as hyperthermia, chills, altered white blood cell count, tachycardia, and/or tachypnoea, as well as worsening liver function, hepatic encephalopathy, shock, renal failure, and gastrointestinal bleeding may also be associated. Notably, however, SBP can be asymptomatic, especially in outpatients [4].

SBP is typically diagnosed through the ascitic fluid Polymorphonuclear Neutrophil (PMN) count where a count greater than 250 per mm^3 with a positive culture obtained in the absence of an intra-abdominal source of infection indicates the condition [4].

Surprisingly, ascitic fluid culture tests when performed in patients with suspected SBP, negative results are yielded in 60% of cases. Manual microscopy, though portrayed as the gold standard for ascitic neutrophil counting, it suffers from being labour-intensive, time-consuming, and expensive, and is associated with inter-observer variability. Although an ascitic fluid culture is required to guide antibiotic therapy, culture negative SBP is defined as an ascitic fluid having neutrophil count of less than 250 cells/mm^3 and negative culture [5].

Owing to high recurrence rates of SBP, multiple antibiotic regimens with different dosing schedules are generally employed for primary and secondary prophylaxis to prevent SBP effectively which becomes decisive for improving the survival and quality of life. Daily administration of twice-daily dose of norfloxacin 400 mg has been shown to reduce the incidence of SBP and enhance 1-year survival rates to 60%, as compared to 48% in the no-prevention group [3, 6].

Consequently, norfloxacin has emerged as the contemporary first-line prophylactic agent against SBP in cirrhotic patients. Nevertheless, norfloxacin needs to be consumed on a daily basis. Selective intestinal decontamination with this drug may culminate into the emergence of resistant gut flora and, consequently, SBP [7].

In this situation, intestinal decontamination using rifaximin has arisen as an encouraging approach for preventing the recurrence of SBP. Rifaximin has displayed its ability in improving transplant-free survival in cirrhotic patients with ascites and preventing the first episode of SBP in cirrhotic patients with ascites [8]. Rifaximin establishes itself as analmost ideal prophylactic antibiotic ascribable to its low systemic absorption rate, broad spectrum coverage (including both gram-negative and gram-positive organisms), and lack of promoting resistance emergence. Additionally, rifaximin is observed to be more effective against gram-positive bacteria as compared to norfloxacin [3, 9].

The present study aimed to compare the success of norfloxacin and rifaximin in the prophylaxis of SBP in patients with Child Pugh Score (CPS)-C cirrhosis, and in preventing the recurrence of SBP in such patients with an objective of assessment of the efficacy of rifaximin in preventing the development of hepatic encephalopathy in these patients.

Material and Methods

This randomized controlled trial was undertaken at a tertiary care hospital in Pune, India. The study population consisted of Outpatient Department (OPD) and Inpatient Department (IPD) patients who were diagnosed with cirrhosis and ascites. The study included all patients over 18 years of age and fulfilling the inclusion criteria, which required patients to have ascitic fluid total protein levels below 1.5 g/dl and meet at least one of the following criteria: CPS above 9 and serum bilirubin levels above 3 mg/dl, serum creatinine levels above 1.2 mg/dl, Blood Urea Nitrogen (BUN) levels above 25 mg/dl, or serum sodium levels below 130 meq/l. The sample size for each group was 33 patients, which was collected with simple random technique. Patients who were allergic to quinolones, diagnosed with hepatocellular carcinoma,

had infections other than SBP and pregnant women were excluded from the study.

After the institutional ethics committee approval, cirrhosis patients with ascites were selected and their CPS were evaluated. Patients admitted in the ward and patients reporting at OPD were screened. Patients with CPS >9 were shortlisted. Ascitic fluid analysis for the shortlisted patients were referred for total leucocyte count, differential count, total protein, albumin as well as Renal Function Tests (RFT), Liver Function Test (LFT), ultrasonography of abdomen and other basic work up as per need. After such clinical and laboratory evaluation, patients fulfilling the inclusion criteria were shortlisted as a part of our study and were randomized into two groups usinga random number table. In Group A patients, 400 mg norfloxacin twice daily per orally for 3 months was administered. Patients in Group B received rifaximin 800 mg (in 2 divided doses) orally after meal (morning and evening) for 3 months.

Follow up of all patients was undertaken every month for 3 months. During every follow up visit, the patients were evaluated clinically for signs, symptoms, and any other complications like hepatic encephalopathy, hepatorenal syndrome and gastrointestinal bleed. The patients displaying the signs and symptoms or complications were further assessed for SBP.

Additionally, any patient under evaluation admitted for any complications related to cirrhosis was evaluated for SBP. During their hospitalisation, if development of hepatorenal syndrome, hepatic encephalopathy, abdominal pain or fever was noted, they were assessed for SBP.

Patients in both Group A and Group B were compared for the number of SBP episodes, SBP induced complications and frequency of hospitalisation. The data collected from such evaluations was analysed using Statistical Package for Social Sciences (SSPS) software, version 26.0.

Descriptive statistics were used to present the results of continuous variables, while frequency and percentages were used to present the results of categorical variables. To compare the groups, chi-square test was used for categorical variables. The student't' test was used for continuous variables. Value of p less than 0.05 was considered to be significant. The study was registered with Clinical Trials Registry-India (CTRI) and the number is REF/2021/01/040197.

Results

A total of 66 cirrhosis patients with ascites and CPS >9 were included in the study. The mean age of the patients was 48.48 ± 10.44 years, ranging between 27 to 78 years. Among the evaluated 66 patients, majority were males -51 (77.3%).

The mean age of patients treated with norfloxacin and rifaximin were 46.42 ± 9.82 and 50.55 ± 10.48 years, respectively and this difference was not statistically significant (p = 0.1034). Additionally, 27 male (81.8%) and 6 female patients (18%) were clubbed in the Group A, while 24 male patients (72.7%) and 9 female patients (27%) were assigned in the Group B, specifying that statistically significant (p = 0.5569) difference in gender distribution between the two groups was not maintained.

Table 1 shows that the most common symptoms reported by the patients consuming norfloxacin and rifaximin were abdominal distension and generalized weakness [31 patients from the norfloxacin group (Group A) and 28 patients from the rifaximin group (Group A)]. The other symptoms were as shown in Table 1.

Table 1: Signs and symptoms among the study groups after consuming norfloxacin and rifaximindoses

Symptoms	Patient numbers		
	Group A (Norfloxacin)	Group A (Rifaximin)	Grand Total
Generalized weakness	31	28	59
Abdominal distension	33	33	66
Scrotal swelling	1	2	3
Chest pain/discomfort	4	3	7
Oliguria	5	2	7
Yellowish discoloration of eye	15	15	30
Burning micturition	2	5	7
Yellowish discoloration of urine	15	14	29
Abdominal pain/discomfort	30	29	59
Breathlessness	22	20	42
Haematuria	1	1	2
Nausea	16	18	34
Vomiting	11	10	21
Decreased appetite	31	29	60
Malena	10	6	16

The etiology of SBP in the study population is represented in Table 2 with majority (75.76%) having Alcoholic Liver Disease (ALD) as the underlying cause. Cryptogenic liver disease, HBsAg positivity, and Non-Alcoholic Fatty Liver Disease (NAFLD) were the other etiologies reported in these patients.The comparison of the hematological parameters for both the patient groups is shown in Table 3. The mean International Normalized Ratio (INR) for patients administered norfloxacin was 2.18 ± 0.51, while for patients consuming rifaximin, it was 1.95 ± 0.48 and this difference was statistically significant ($p = 0.0218$) (Table 3).

Table 2: Etiology of SBP in study population

Etiology	Frequency (N)	Percentage (%)
ALD	50	75.76
Cryptogenic liver disease	6	9.09
HBsAg positive	4	6.06
NAFLD	3	4.55
Alcohol hepatitis	1	1.52
HCV Positive	1	1.52
NASH	1	1.52
Total	66	100.00

ALD: Alcoholic liver disease, NAFLD: Non-alcoholic fatty liver disease, HCV: Hepatitis C virus, NASH: Non-alcoholic steatohepatitis

Table 3: Comparison of hematological parameters between norfloxacin and rifaximin consuming patient groups

Hematological Parameters	Norfloxacin	Rifaximin	*p*
Hemoglobin	8.72 ± 2.12	9.61 ± 2.05	0.0762
TLC (×100)	8660.61 ± 4768.77	10018.18 ± 5760.50	0.9999
Platelet (×1000)	106545.45 ± 59772.53	127296.97 ± 78385.97	0.9999
PT	24.36 ± 6.99	22.06 ± 6.54	0.3625
INR	2.18 ± 0.51	1.95 ± 0.48	0.0218*

TLC: Total Leukocyte Count, PT: Prothrombin time, INR: International normalized ratio

The biochemical parameters such as LFTs and ascitic fluid examination were compared in both the patient groups and no significant difference was found (Figure 1). At the first follow-up stage after one month, 31 patients continued with norfloxacin while 33 continued with rifaximin (Figure 2). Five and three patients from the norfloxacin (Group A) and rifaximin (Group B) groups, respectively, reported the history of hospitalization. In the Group A patients, hepatic encephalopathy, GI bleed, hepatorenal syndrome, and episode of SBP were reported by 15.2%, 15.2%, 12.1%, and 24.2% of patients, respectively, while in the Group B patients, the corresponding numbers were 6.1%, 12.1%, 3%, and 9.1%. One patient consuming norfloxacin (Group A) was non-adherent and the other was lost to follow-up.

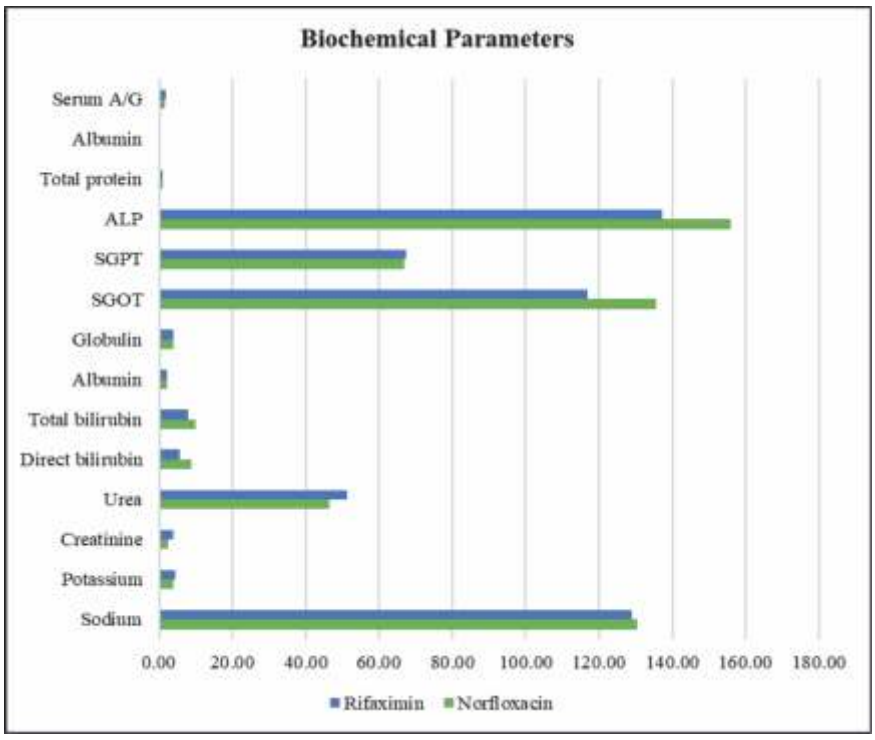

Figure 1: Comparison of biochemical parameters between two patient groups, one consuming norfloxacin and the other consuming rifaximin (ALP: Alanine aminotransferase, SGPT: Serum glutamic pyruvic transaminase, SGOT: Serum glutamic-oxaloacetic transaminase)

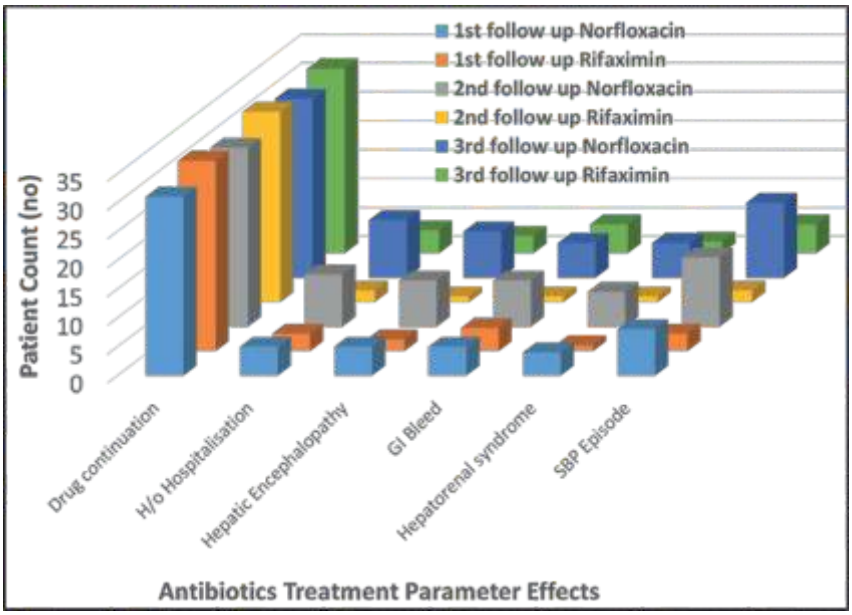

Figure 2: Comparison of antibiotic treatment parameters between two patient groups, one consuming norfloxacin and the other consuming rifaximin at 1st, 2nd and 3rd follow-up stage

During the second follow-up after two months, 31 patients were found to continue with norfloxacin and 33 with rifaximin. Nine patients consuming norfloxacin (Group A) and two consuming rifaximin (Group B) reported history of hospitalization. From the Group A patients, hepatic encephalopathy, GI bleed, hepatorenal syndrome, and episode of SBP were reported by 24.2%, 24.2%, 18.2%, and 36.4% of patients respectively. In Group B, the corresponding numbers were 3%, 3%, 3%, and 6.1%.

During the third follow-up after three months, 31 patients continued with norfloxacin and 32 with rifaximin. Ten patients from Group A and four from Group B reported history of hospitalization. From Group A, hepatic encephalopathy, GI bleed, hepatorenal syndrome, and episode of SBP were reported by 24.2%, 18.2%, 18.2%, and 39.4% of patients, respectively. Whereas, for Group B patients, the corresponding numbers were 9.1%, 15.2%, 6.1%, and 15.2%. One patient from the Group B was lost to the third follow-up.

Discussion

SBP is a common and grave complication in patients with cirrhosis and ascites. SBP occurs due to compromised bactericidal activity in the ascitic fluid and prolonged bacteremia arising from weakened host defences [10]. Gram-negative aerobic bacteria, particularly *Escherichia coli*, are accountable for more than 75% of SBP infections [5, 11-13]. Nearly 70% of SBP cases occur in patients with CPS C [14]. Over the years, infection-related mortality ascribable to SBP has been reported to gradually decrease due to timely detection and a wider range of effective antibiotics [15]. Prevention of SBP is decisive in improving the prognosis of cirrhotic patients, however the optimal prophylactic antibiotic strategy yet remains tentative [16-17].

The present study evaluated the efficacy of norfloxacin and rifaximin in preventing SBP in cirrhotic patients with ascites and CPS >9. The results established that both norfloxacin and rifaximin were effectual in the occurrence reduction of SBP, with no substantial difference between the two patient groups in terms of age and gender distribution. The most common symptom reported by all patients was abdominal distension which propounded that ascites was the main problem in these patients. Generalized weakness was another major symptom reported by large number of patients from both groups, specifying the similar effect of both drugs on the overall health status of the patients. Yellowish discoloration of the eyes as well as urine were also commonly reported symptoms by the patients, hinting at the presence of hyperbilirubinemia, which is frequently observed in cirrhotic patients.

The incidence of other signs such as scrotal swelling, chest pain or discomfort, oliguria, and burning micturition were reported by relatively lesser number of patients from both groups. Such signs are usually ascribable to the complications of cirrhosis like hepatorenal syndrome, urinary tract infection, and hepatic encephalopathy.The low reported incidence of these signs in both patient groups affirmed that both norfloxacin and rifaximin were significantly efficacious in averting these complications.

Two studies reported the comparison of the efficiency of norfloxacin and rifaximin in treating cirrhosis patients with ascites and similar CPS. Chao *et al.,* (2017) studied two patient groups of 43 each with similar age, sex, and CPS classification, and found similar proportions of patients with CPS

B and C [18]. Ghafar *et al.,* (2019) carried out similar study on 80 patients by dividing them into two groups (with similar mean age), where one was administered rifaximin + norfloxacin, and the other only norfloxacin [19]. The most reported adverse effects of norfloxacin were gastrointestinal symptoms, headache, dizziness, and asthenia, while the most reported adverse effects of rifaximin were gastrointestinal symptoms and generalized weakness or fatigue [20].

As far as laboratory parameters were concerned, no significant differences were reported between the two groups in platelet count, total leukocyte count, and mean hemoglobin levels. These reported findings also approve our findings that both norfloxacin and rifaximin exhibit similar effects on the hematological profile of patients with cirrhosis and ascites. However, it is noteworthy that the mean hemoglobin levels for patients from both groups were below the normal range, pointing at the presence of anemia, a common complication of cirrhosis.

Similar mean Prothrombin Time (PT) was observed for both the patient groups, indicating that the effect of both norfloxacin and rifaximin was similar on coagulation function. On the contrary, considerably higher mean INR was noted in the patients from norfloxacin group, indicating a higher risk of bleeding. Therefore, it becomes very essential to monitor the coagulation function of patients consuming norfloxacin, especially for those with a history of bleeding or already on anticoagulant medications.

The results of the present study found ALD as the most common etiology of SBP in the study population, accounting for almost 76% of cases. Interestingly, a significant proportion (9.09%) of patients from this study exhibited cryptogenic liver disease as the underlying cause for SBP. The relatively low prevalence of HBsAg positivity and Hepatitis C Virus (HCV) positivity as etiologies of SBP in this study reflected the success of vaccination and antiviral treatment programs in reducing the burden of viral hepatitis in the study population.

The study also carried out the comparison of biochemical parameters between patients advised norfloxacin and rifaximin for the primary prevention of SBP and no significant difference in haemoglobin levels, total leukocyte count, platelet count, and PT was noted. However, a significant difference in the INR was seen between the two patient groups, with patients consuming norfloxacin showing a higher INR than those taking rifaximin. Furthermore, the study compared the LFT and ascitic fluid examination parameters between the two patient groups and no significant difference was found out. These results promulgated that both norfloxacin and rifaximin were equally effective in the prevention of SBP in patients with cirrhosis.

In the study carried out by Praharaj *et al.*, (2022) baseline characteristics were similar between norfloxacin and rifaximin patient groups except for low serum albumin levels in the former group [21]. Ghafar *et al.,* (2019) also observed that there was no significant difference between patient groups consuming rifaximin + norfloxacin versus norfloxacin alone groups [19]. Shamseya *et al.,* (2016) reported that SBP patients exhibited significantly higher baseline values for serum bilirubin, PT, and CPS, with no significant difference in SBP occurrence between rifaximin and norfloxacin patient groups [20]. Narang *et al*., (2018) noted

higher baseline values for serum bilirubin, PT, and CPS, in SBP patients compared to non-SBP patients, with comparable ascitic fluid total protein and RFT in both patient groups [22]. Chao *et al.,* (2017) found comparable RFT, ascitic fluid albumin concentration, and baseline liver profile values in both patient groups consuming rifaximin and norfloxacin [18].

SBP, a notorious complication in cirrhotic patients, affects 7 to 30% of hospitalized patients and has high mortality rates[17, 23]. Primary antibiotic prophylaxis of SBP is recommended for patients with low ascitic fluid protein, CPS of 9, and bilirubin level of 3 mg/dl, renal dysfunction, and hyponatremia [24]. Third generation cephalosporins are the favoured antibiotic drugs for empirical therapy owing to their broad-spectrum activity, efficacy, and safety. Medical fraternity recommends to initiate empirical therapy without delay while waiting for the precise organism to be identified [12]. Notwithstanding previous studies claiming substantial drop in SBP occurrence or recurrence with antibiotic prophylaxis, current European Association for the Study of the Liver (EASL) guidelines recommend prophylaxis only for patients at the highest risk of developing SBP [24-26].

A daily dose of 400 mg norfloxacin is the most commonly used antibiotic therapy for both primary and secondary prophylaxis, though other antibiotics such as ceftriaxone, ciprofloxacin, cotrimoxazole, and rifaximin also are being assessed. Among them, rifaximin, a non-systemic, gut-selective oral antimicrobial having broad-spectrum activity, shows miniscule selection for bacterial mutants resistant to rifaximin. Additionally, it is reported to reduce the recurrence of hepatic encephalopathy [27].

The present study compared the efficacy of norfloxacin and rifaximin in preventing complications in patients with cirrhosis and ascites. The results demonstrated that rifaximin was associated with lower incidence rates of hepatic encephalopathy, GI bleed, hepatorenal syndrome, and SBP compared to norfloxacin at both the second and third follow-ups. At the third follow-up, the incidence of SBP was significantly lower in the rifaximin patient group compared to the norfloxacin patient group. However, the only drawback associated with the study was the relatively smaller sample size, and a larger patient group study may be necessary to confirm these findings.

Comparison of efficacy of rifaximin and norfloxacin in preventing SBP and other complications of cirrhosis has been carried in some studies. Narang *et al.,* (2018) reported that rifaximin prophylaxis caused fewer SBP episodes as compared to norfloxacin in patients consuming these medicines [22]. Chao *et al.,* (2017) and Shamseya *et al.,* (2016) reported lesser number of hepatic encephalopathy episodes in the patient group consuming rifaximin [18, 20]. Praharaj *et al.,* (2022) noted relatively better efficacy of rifaximin in preventing SBP in secondary prophylaxis [21]. Saleh *et al.,* (2019) observed that rifaximin combined with norfloxacin led to substantial improvement in primary SBP prevention [28]. Assem *et al.,* (2016) reported that norfloxacin and rifaximin combination was superior to norfloxacin alone in primary prophylaxis for SBP [29]. Ghafar *et al.,* (2019) also observed drastic reduction in incidence of SBP in the patient group receiving rifaximin and norfloxacin combination than in the group receiving only norfloxacin. Finally, Mostafa *et al.,*

(2015) also noted a numerical advantage for rifaximin in preventing the occurrence of SBP [30].

Conclusion

This study successfully demonstrated lower incidences of hepatic encephalopathy, GI bleeding, hepatorenal syndrome, and SBP in patients with cirrhosis and ascitesin the patients consuming rifaximin as compared to norfloxacin. Additionally, such patients reported fewer hospitalizations and better overall outcomes. These findings propose rifaximin as a more effective treatment option for preventing SBP related complications in this patient population. Nevertheless, further studies with larger sample sizes and longer follow-up periods are essential to further assert these results.

Acknowledgements

The authors acknowledge the support received from the management of BVDU, Pune and from the Medical College of BVDU, Pune.

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How to cite this article:
Pala S, Doke P, Maindad D. Norfloxacin versus rifaximin for spontaneous bacterial peritonitis prophylaxis: A randomized controlled trial. *J Krishna Inst Med Sci Univ* 2024; 13(1):112-122.

Submitted: *20-Oct-2023* ***Accepted:*** *21-Dec-2023* ***Published:*** *01-Jan-2024*