Original Article

# A Prospective Study On Rifaximin's Activity And Immunomodulatory Impact In Prophylaxis Of Spontaneous Bacterial Peritonitis In Cirrhotic Pakistani Population

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## Abstract

**Aims:** The purpose of this study was to assess rifaximin's effectiveness and immunomodulatory effects as another possible preventative treatment for cirrhotics' spontaneous bacterial peritonitis (SBP).

**Methods:** The design of this study was a prospective study design. This study was conducted at shaikh Zayed Hospital Lahore and the duration of this study was from July 2021 to May 2022. The research comprised 50 individuals with ascites and cirrhosis. In a randomised single-blind way, the patients were split into two groups. Rifaximin was given to group one (n=30), while norfloxacin was given to group two (n=20). The course of therapy lasted six months. The main inflammatory indicators employed in the study to assess the impact of the drugs used were serum levels of tumour necrosis factor alpha (TNF-), interleukin-6 (IL-6), and interleukin-10 (IL-10).

**Results:** Five patients receiving norfloxacin therapy demonstrated spontaneous bacterial peritonitis three months after treatment, however all cases receiving rifaxine therapy were spontaneous bacterial peritonitis -free. TNF-, IL-6, and IL-10 blood levels did not significantly differ between individuals receiving rifaximin and norfloxacin treatment ($p>0.05$). The blood levels of TNF- and IL-6 in patients receiving treatment with rifaximin and norfloxacin both decreased statistically significantly from baseline values ($p=0.000$ and $p=0.000$, respectively). In contrast, serum IL-10 increased in both groups compared to baseline ($p>0.00$) in a statistically significant manner. Those receiving rifaximin therapy had a more successful remission from spontaneous bacterial peritonitis six months after treatment than those receiving norfloxacin medication.

**Conclusion:** In the conclusion of this study, the usage of rifaximin in spontaneous bacterial peritonitis patients not only stops bacterial translocation but also regulates the immune system's production of pro- and anti-inflammatory cytokines. Rifaximin's effectiveness and immunomodulatory impact in the prevention of spontaneous bacterial peritonitis in cirrhotics, however, need more prospective large-scale, double-blind investigations.

**KEYWORDS:** Immune System, Norfloxacin, Spontaneous Bacterial Peritonitis, Rifaximin, Inflammatory Cytokines

## INTRODUCTION

The most prevalent and potentially fatal infection in people with liver cirrhosis, spontaneous bacterial peritonitis (SBP), has to be promptly identified and treated. spontaneous bacterial peritonitis is now linked to in-hospital mortality rates between 20% to 40% (1). Additionally, death rates were found to be 50%-70% and 70%-75%,

respectively, 1 and 2 years following an episode of spontaneous bacterial peritonitis. Nevertheless, the mortality rate from spontaneous bacterial peritonitis was reduced by fast treatment with empiric antibiotics and early diagnosis (2). The primary mechanism in the pathophysiology of spontaneous bacterial peritonitis has been proposed to be bacterial translocation (BT), which is the movement of living microorganisms from the intestinal lumen to the mesenteric lymph nodes and other extra-intestinal locations. In this study, it is shown that bacterial translocation and IBO in experimental and human cirrhosis are reduced by selective intestinal decontamination (SID) using less absorbable antibiotics, hence preventing spontaneous bacterial peritonitis (3,4). Antibiotics taken as a preventative measure lower the danger of spontaneous bacterial peritonitis recurrence. According to recommendations from the European Association for the Study of the Liver (EASL), norfloxacin (400 mg/day, orally) is the preferred therapy.

The gastrointestinal system is where the oral antibacterial medication rifaximin is mostly absorbed. It has a minimal risk of causing bacterial resistance and broad-spectrum in vitro action against gram-positive and gram-negative aerobic and anaerobic enteric bacteria (5). Rifaximin's poor systemic bioavailability may make it more suitable for long-term usage than other antibiotics with negative side effects that are more bioavailable. Overall, using a single antibiotic continuously does not seem to be the best option, hence efforts should be made to find alternatives, such as antibiotic cycling (6,7). The current study evaluated the effectiveness of rifaximin when taken orally as a potential preventative treatment for spontaneous bacterial peritonitis in cirrhotic individuals. Also, baseline levels of both pro- and anti-inflammatory cytokines were assessed both before and after therapy.

## MATERIALS AND METHODS

The design of this study was a prospective study design. This study was conducted at shaikh Zayed Hospital Lahore and the duration of this study was from July 2021 to May 2022. 65 individuals with cirrhosis and ascites who had at least one prior episode of spontaneous bacterial peritonitis were included in this prospective research. Cirrhosis was diagnosed using clinical, biochemical, and histological standards. Participants provided written informed permission and met the age requirements of >20 and 65. If the polymorphonuclear cell (PMN) count in the ascitic fluid was greater than 250 mm3 with or without a positive culture and there was no intra-abdominal infection source, the diagnosis of spontaneous bacterial peritonitis was established. The traditional technique and the bedside inoculation of 10 ml of fluid in aerobic and anaerobic blood culture bottles were used to produce ascitic fluid cultures.

Active gastrointestinal bleeding, encephalopathy (>grade 2), hepatocarcinoma or other malignancies, and drug allergy were the exclusion criteria. 15 individuals were enrolled but were later removed from this research (10 patients had hepatocellular carcinoma, and five patients had severe gastrointestinal bleeding; who subsequently died). The trial included 50 patients, who were split into two groups. Group one (n = 30) got 800 mg of rifaximin orally daily for six months, whereas group two (n = 20) received 400 mg of norfloxacin orally daily for six months. All of the research participants' cirrhosis was caused by viral hepatitis C. Child-Pugh classification, which assigns all patients a Child C rating, was used to assess liver function.

Red and white blood cell, platelet, haemoglobin, prothrombin time, and serum TNF-, IL-6, and IL10 concentrations were determined at baseline and six months after therapy during the physical examination, liver and renal function tests, admission, and admission visit. Every month, patients were carefully monitored in order to rule out any problems, including fever, stomach discomfort, or other symptoms or signs of infection. When spontaneous bacterial peritonitis returned, which served as the trial's endpoint, the study drug was stopped. Patients experiencing further issues, such as gastrointestinal bleeding or encephalopathy, had the study medications stopped, and they were then given a routine course of treatment that is appropriate in each situation. Each patient had a sterile venipuncture performed using disposable syringes, without foaming, and after a brief period of venous stasis to get approximately 10 ml of blood from them. A vacutainer serum separator tube containing around 3 ml of venous blood was used for the delivery. The sample was immediately centrifuged at 3000 rpm to prevent erythrocyte arginase contamination, and then serum samples were utilised for liver and renal function testing. Each patient had a sterile venipuncture performed using disposable syringes, without foaming, and after a brief period of venous stasis to get approximately 10 ml of blood from them. A vacutainer serum

separator tube containing around 3 ml of venous blood was used for the delivery. The sample was immediately centrifuged at 3000 rpm to prevent erythrocyte arginase contamination, and then serum samples were utilised for liver and renal function testing.

Using urease and glutamate dehydrogenase, blood urea nitrogen was measured spectrophotometrically utilising the enzymatic (fixed rate) UV technique. Spectrophotometric measurement of serum creatinine concentration was performed using the buffered kinetic Jaffé reaction without deproteinization technique. A graduated vacutainer plastic tube containing 2 mL of venous blood and 3.6 mg of potassium ethylene diamine tetra acetic acid (K-EDTA) was used to test the patient's complete blood count (CBC), haemoglobin (Hb), white blood cells (WBCs), red blood cells (RBCs), and platelets (PLTs). For the purpose of measuring TNF-, IL-6, and IL-10, 3 mL of venous blood were collected into EDTA tubes containing the protease inhibitor aprotinin. Before collecting blood samples, these tubes were kept chilled. When blood was drawn, the serum was separated within 30 minutes, and it was stored frozen at 70°C for TNF-, IL-6, and IL-10 measurements. Sandwiched ELISA was used to measure the levels of TNF-, IL-6, and IL-10 in the blood using the e Bioscience Human TNF-, Human IL-6, and Human IL-10 platinum ELISA BMS213/2/BMS213/2TEN, BMS 215/2/ BMS212/2 TEN, and Biotek Elx 800-UV microtiter plate reader, respectively. The sample size was determined using data from the previous trial and the presumption that norfloxacin prophylaxis prevented infection. With an alpha error of 0.05 and a 95% confidence level, the data were statistically analysed. The data were expressed as mean $\pm$SD. Continuous data were assessed using the chi-square test, which contrasts nominal parameters, and the t-test, which is required for quantitative variables. The statistical analysis was completed using IBM SPSS Statistics V 20.

## RESULTS

To this investigation, 50 cirrhotic individuals were randomly assigned. Table 1 shows the participant's demographic information, including age, sex, weight, smoking, and scores for the Child-Pugh and Model for End-Stage Liver Disease (MELD) tests as well as indicators for hepatic encephalopathy and other concurrent medications.

**Table 1. Demographic Data of The Participants**

| **Parameters** | **Rifaximin** | **Norfloxacin** | **P-Value** |
|---|---|---|---|
| **(n=30)** | | | |
| Age (years) | 55.8±4.81 | 56.5±4.17 | 0.50 |
| Sex (male) | 20 (90%) | 16 (88%) | 0.829 |
| Weight (kilograms) | 80.6±6.26 | 80.7±7.16 | 0.740 |
| Smoking (%) | 3 (14%) | 2 (11%) | 0.533 |
| Diabetes (%) | 3 (14%) | 2 (11%) | 0.533 |
| Hypertension (%) | 4 (18%) | 2 (11%) | 0.423 |
| Child-Pugh score | 10.25±1.1 | 10.67±1.8 | 0.54 |
| MELD score | 17.1±4.2 | 16.25±4.9 | 0.417 |
| Hepatic encephalopathy | 7 (17%) | 5 (20%) | 0.43 |
| Concomitant medication uses during the study % | | | |
| Spironolactone | 38 (95%) | 24 (96%) | 0.956 |
| Furosemide | 36 (90%) | 23 (92%) | 0.94 |

| | | | |
|---|---|---|---|
| Propranolol | 5 (12.5%) | 3 (12%) | 0.988 |

Both groups did not report any severe negative side effects. Patients taking norfloxacin reported just a few minor side effects, including three cases of nausea (10%) and two cases of headache (6.6%). These side effects were symptomatically addressed, and patient follow-up confirmed that they had vanished. Those on rifaximin, however, did not report any side effects. Test results for the liver, kidneys, complete blood count, and serum levels of TNF-, IL-6, and IL-10 at baseline did not significantly differ between the two groups ($p>0.05$). As a result, as shown in Table 2, any changes that developed following treatments were attributed to the medication's effects and not to individual variances. Table 3 shows the laboratory features of patients six months following therapy, expressed as mean $\pm$SD.

Five patients receiving norfloxacin treatment demonstrated spontaneous bacterial peritonitis (5/20 or 16.6%) three months following the start of the medication. Nevertheless, none of the subjects receiving rifaxine medication had spontaneous bacterial peritonitis (0/30 or 0%). Gram-positive cocci were found to be present in the ascitic fluid of the five infected individuals. All spontaneous bacterial peritonitis patients were removed from the research and given third-generation cephalosporin, which had a very good prognosis.

**Table 2. Features Of Patients at Baseline**

| Parameters | Rifaximin | Norfloxacin | P-Value |
|---|---|---|---|
| AST (IU/L) | 74.90±14.28 | 79.80±13.63 | 0.979 |
| ALT (IU/L) | 52.40±14.27 | 55.90±10.29 | 0.862 |
| BIL-T (mg/dL) | 2.46±0.90 | 2.36±0.63 | 0.321 |
| BIL-D (mg/dL) | 1.11±0.37 | 1.10±0.29 | 0.238 |
| Albumin (g/dL) | 2.55±0.37 | 2.75±0.35 | 0.810 |
| PT, INR | 2.37±0.56 | 2.33±0.46 | 0.359 |
| BUN (mg/dL) | 57.2±20.83 | 58.1±20.14 | 0.885 |
| s.Cr (mg/dL) | 1.70±0.25 | 1.68±0.45 | 0.226 |
| Hemoglobin (g/dL) | 9.11±0.92 | 9.03±1.16 | 0.438 |
| RBCs ($10^6$ /uL) | 3.22±0.51 | 3.39±0.43 | 0.673 |
| WBCs ($10^3$ /uL) | 8.37±2.70 | 8.71±2.83 | 0.863 |
| Platelets ($10^3$ /uL) | 74.96±15.24 | 76.96±10.45 | 0.156 |
| TNF-α (pg/mL) | 186.67±31.05 | 182.28±27.48 | 0.670 |
| IL-6 (pg/mL) | 174.98±33.58 | 170.11±33.49 | 0.614 |
| IL-10 (pg/mL) | 35.05±6.17 | 39.12±6.44 | 0.911 |

**Table 3. Features Of Patients Six Months After Treatment**

| Parameters | Rifaximin | Norfloxacin | P-Value |
|---|---|---|---|
| AST (IU/L) | 78.1±10.65 | 82.50±10.48 | 0.921 |
| ALT (IU/L) | 54.40±11.62 | 50.40±8.75 | 0.272 |
| BIL-T (mg/dL) | 2.72±0.77 | 2.60±0.65 | 0.750 |
| BIL-D (mg/dL) | 1.31±0.44 | 1.13±0.28 | 0.417 |

| | | | |
|---|---|---|---|
| Albumin (g/dL) | 2.63±0.30 | 2.66±0.22 | 0.558 |
| PT, INR | 2.38±0.33 | 2.43±0.54 | 0.400 |
| BUN (mg/dL) | 55.4±14.52 | 56.1±9.60 | 0.133 |
| s.Cr (mg/dL) | 1.46±0.24 | 1.48±0.30 | 0.543 |
| Hemoglobin (g/dL) | 9.01±0.78 | 8.77±0.64 | 0.329 |
| RBCs ($10^6$/uL) | 3.39±0.25 | 3.28±0.37 | 0.216 |
| WBCs ($10^3$/uL) | 6.90±2.52 | 7.67±2.03 | 0.793 |
| Platelets ($10^3$/uL) | 74.43±12.31 | 75.33±5.86 | 0.096 |
| TNF-α (pg/mL) | 93.29±17.56 | 90.88±14.03 | 0.175 |
| IL-6 (pg/mL) | 90.45±17.87 | 83.83±16.12 | 0.063 |
| IL-10 (pg/mL) | 87.02±13.87 | 90.45±17.87 | 0.579 |

The levels of TNF-, IL-6, and IL-10 in the blood were not statistically different between the rifaximin and norfloxacin groups six months after therapy (p>0.05). Six months after starting therapy, TNF- and IL-6 levels in the rifaximin group were statistically significantly lower than their baseline levels (p=0.000 and p=0.000, respectively). Moreover, as compared to its baseline data, the blood IL-10 level revealed a statistically significant rise (p=0.000). Six months following therapy, TNF- and IL-6 levels in the norfloxacin group were statistically significantly lower than their baseline levels (p=0.000 and p=0.000, respectively). Yet, as compared to baseline data, the serum IL-10 level exhibited a statistically significant rise (p=0.000).

Serum creatinine levels in the rifaximin and norfloxacin groups revealed a noticeable fall in levels by around 14.09% and 11.46%, respectively, six months after therapy, compared to baseline data. Moreover, there was no statistically significant difference in serum creatinine levels between the two research groups.

## DISCUSSION

In patients with community-acquired sepsis, anti-inflammatory cytokines have been shown to be helpful diagnostic and prognostic markers. Serum levels of TNF-, IL-6, and IL-10 were the main inflammatory indicators employed in this commentary's research to gauge how well the prescribed drugs worked (8,10). Our study's findings demonstrated that rifaximin treatment decreased spontaneous bacterial peritonitis episodes in cirrhotics. Our results unmistakably showed that intestinal cleansing with rifaximin caused mean blood levels of the pro-inflammatory cytokines (TNF- and IL-6) to significantly decrease (11,12), while the serum level of the anti-inflammatory cytokine increased (IL-10). The cause of spontaneous bacterial peritonitis episodes returning in individuals receiving norfloxacin therapy was gram-positive organisms that are resistant to this medication.

Both rifaximin and norfloxacin reduced serum TNF- and IL-6 levels relative to baseline in a statistically significant manner. Moreover, 6 months after therapy, there was a statistically significant rise in IL-10 blood levels in both groups (13). Rifaximin and norfloxacin both had an impact on serum TNF- and IL-6 levels, which is consistent with earlier research that showed selective intestinal decontamination as a secondary prophylaxis of spontaneous bacterial peritonitis not only eliminates bacterial products but also regulates patients' pro-inflammatory response (14,15,8).

The direct cellular influence on neutrophil response to oxidative stress by decreasing reactive oxygen species production and raising the apoptosis rate is what causes the immunomodulatory effect. On the other hand, the rise in IL-10 levels in the serum is consistent with Go' Mez-Hurtadog et al (2011), observation that selective intestinal decontamination patients had considerably higher IL-10 levels (16).

Also, it was proposed that IL-10 is in charge of the anti-inflammatory response in cirrhotic patients receiving norfloxacin for the secondary prevention of spontaneous bacterial peritonitis (17). The previously reported finding that IL-10 has been found to downregulate a number of different macrophage functions, including cytokine

production TNF-, IL-1, and IL-6, could be used to explain the rise in serum IL-10 levels and the decrease in both serum IL-6 and TNF- levels in patients undergoing selective intestinal decontamination (18,9). The results of this study shown that the anti-inflammatory cytokine IL-10 level may be utilised as a suitable diagnostic and prognostic marker for spontaneous bacterial peritonitis in cirrhotics and might be of comparable value to the pro-inflammatory cytokines in determining the degree of disease in spontaneous bacterial peritonitis (10,20).

Escherichia coli is the most frequently isolated microorganism from cases of spontaneous bacterial peritonitis, and it has been demonstrated that taking 800 mg of rifaximin for 5 days significantly lowers the population of faecal Escherichia coli. Therefore, rifaximin intake during the current study was based on this fact (400 mg/twice daily, orally) (21). Rifaximin outperformed norfloxacin in the current prospective research because it is essentially non-absorbable, which reduces the development of antimicrobial resistance and preserves the drug's safety across all patient populations. Additionally, rifaximin outperforms norfloxacin in its ability to combat gram-positive bacteria. This is extremely crucial, especially given the rise in gram-positive bacteria in spontaneous bacterial peritonitis (10).

The decrease in bacterial translocation and consequent correction of hemodynamic abnormalities, which lowers the risk of bleeding, encephalopathy, and infections, may be responsible for the increase in survival seen in the current research. The absence of mortality seen in this study might be due to the shorter follow-up in our study (6 months) (22).

This study's findings showed that rifaximin sustained spontaneous bacterial peritonitis remission more successfully than norfloxacin. Rifaximin may therefore be preferable when a doctor decides to administer a poorly absorbable antibiotic for the prevention of an episode of spontaneous bacterial peritonitis (5). Rifaximin is used as a selective intestinal decontamination to treat spontaneous bacterial peritonitis patients, and it not only prevents bacterial translocation but also alters the immune system's production of pro- and anti-inflammatory cytokines (23). When determining the severity of the sickness in spontaneous bacterial peritonitis, the anti-inflammatory cytokine IL-10 may be just as important as the pro-inflammatory cytokines (IL-6 and TNF-). Further prospective large-scale double-blind trials are required to determine the effectiveness and immunomodulatory impact of rifaximin in the prevention of spontaneous bacterial peritonitis in cirrhotics. The study's limitations may include its small sample size and brief follow-up time. As a result, this work requires more extension and investigation.

## CONCLUSION

In the conclusion of this study, the usage of rifaximin in spontaneous bacterial peritonitis patients not only stops bacterial translocation but also regulates the immune system's production of pro- and anti-inflammatory cytokines. Rifaximin's effectiveness and immunomodulatory impact in the prevention of spontaneous bacterial peritonitis in cirrhotics, however, need more prospective large-scale, double-blind investigations.

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