Original Article

Effectiveness of Rifaximin versus Norfloxacin in Prevention of Spontaneous Bacterial Peritonitis in Cirrhotic Patients

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ABSTRACT

Objective: This study aimed to compare the effectiveness of rifaxamin versus norfloxacin in prevention of spontaneous bacterial peritonitis in cirrhotic patients.

Study Design: Randomized Control Trial.

Place and Duration of Study: This study was conducted at the Medical Unit-II, Shaheed Mohtarma Benazir Bhutto Medical University, Larkana from January, 2019 to June, 2019.

Materials and Methods: All patients who fulfilled the inclusion criteria and visited to the Medical unit-II, Chandka Medical College and Hospital, SMBBMU Larkana were included in the study. Informed consent was taken after explaining the procedure, risks and benefits of the study. The total of 244 patients were randomly divided into two groups i.e. (Group A Rifaxamin) and (Group B Norfloxain). Ascitic tap was done to all the patients to see the presence of SBP and blood samples weresent to the laboratory for urea, creatinine, serum sodium, serum bilirubin, serum albumin and PT. Patients were followed over the duration of 6 months and each patient was called for examination after every 3 months to assess the efficacy in term of non-reoccurrence of SBP. All the collected information was recorded on proforma and used electronically for research purpose.

Results: Mean ± SD of age was 37.74±8.75 and 38.89±8.84 years in norfloxacin and rifaximin group respectively. In group wise distribution of gender 64 (52.5%) male and 58 (47.5%) female was enrolled in norfloxacin group and 74 (60.6%) male and 48 (39.4%) female was included in rifaximin group. In comparison of both groups 103(84.4%) efficacy was noted in norfloxacin group whereas 110(90.2%) efficacy was documented in rifaximin groupand p value found to be insignificant i.e. (P=0.178).

Conclusion: As non-significant difference was found between rifaximin versus norfloxacin, so it is to be concluded that rifaximin is an appropriate alternative for long-term primary and secondary prophylaxis of SBP in cirrhotic patients with ascites.

Key Words: Rifaximin, Norfloxacin, Spontaneous Bacterial Peritonitis, Efficacy.

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INTRODUCTION

Cirrhosisaccounts for approximately one million deaths every year [(1)]. It is a characterized by hepatic fibrosis to point that there is architectural distortion with formation of regenerative nodules, representing the final histological change for a variety of chronic liver diseases, clinically manifested by ascites, spontaneous bacterial peritonitis, variceal bleeding and hepatic encephalopathy[(2)].

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Pakistan has second highest estimated prevalence of cirrhosis worldwide secondary to hepatic viral infections specially HCV [(3)]. Cirrhosis is most commonly caused by Alcohol, non-alcoholic fatty liver disease, hepatitis C, hepatitis B and hepatitis D[(4)]. A number of less common causes include autoimmune hepatitis, primary biliary cholangitis, Wilson's disease, hemochromatosisand certain medications. Spontaneous bacterial peritonitis (SBP) is fatal complication of cirrhosis, approximately present in 20 to 30% of patients. However, the incidence is>40% in patients with ascitic fluid total protein <1g/dl [(5)]. American Association for the Study of Liver Diseases Practice Guideline management of adult (AASLD) defines SBP as a development of bacterial infection in the peritoneum causing peritonitis without any evidence of intra-abdominal, surgically treatable source of infection and its diagnosis is made in the presence of an elevated ascitic fluid absolute polymorphonuclear leucocytes (PMNL) count ≥250 cells/mm3. The mortality rate in patients with SBP ranges from 40-70% in adult patients

with Cirrhosis [6].The proposed mechanism for development of SBP is translocation of intestinal bacteria into the ascitic fluid. On surviving an episode of SBP, the recurrence rate is approximately 70% at 1 year [7]. High recurrences coupled with substantial mortality warrants long-term antibiotic prophylaxis to prevent SBP. Various oral antibiotics have been studied to reduce the risk of occurrence and recurrence of SBP by achieving selective intestinal decontamination [8]. The AASLD and European Association for the Study of the Liver (EASL) recommend Norfloxacin, a fluoroquinolone, as the first-line therapy for the prevention of spontaneous bacterial peritonitis [9,10].Extensive use of Norfloxacin for this purpose has increased the incidence of Quinolone-resistant and gram positive SBP[10]. Rifaximin is abroad-spectrum antibiotic and is poorly absorbed systematically, thereby reaches high levels in the gut lumen[11]. The main advantage of Rifaximin is that it is virtually unabsorbed, which minimizes the antimicrobial resistance. In addition, Rifaximin has better activity against gram-positive organism than Norfloxacin. Its role as an initial and add-on therapy for hepatic encephalopathy has been well established [12]. Studies suggest that prevention of SBP with other drugs such as Norfloxacin and trimethoprim-sulfamethoxazole reduce the rate of SBP infections in almost 68% of the patients and with Rifaximin about 89%[13]. Other studies reported the reoccurrence of SBP is significantly lower in the rifaximin group (3.88 vs. 14.13%) compared with the norfloxacin group (P=0.04) [14].

MATERIALS AND METHODS

The Randomized Control Trial study was conducted at Medical Unit-II, Shaheed Mohtarma Benazir Bhutto Medical University, Larkana after approval of ethical review committee from January 13, 2019 to June 12, 2019. Sample size was calculated n=122 in each groupby using W.H.O sample size calculator version 2.0. Patients between age group 25-55 years ofboth genders with cirrhosis in accordance with operational definition, History of variceal bleeding, Child-Pugh score ≥ 9, Serum creatinine > 1.2 mg/dL, BUN > 25mg/dL, Serum sodium < 130mEq/L and serum albumin > 25g/dl were included in study after taking written informed consent. Their ascitic tap was done under the supervision of consultant and blood samples were sent to the laboratory for urea, creatinine, serum sodium, serum bilirubin, serum albumin and PT. The patients were randomly divided into two groups i.e. (Group A Rifaxamin) and (Group B Norfloxain) by using computer-generated sequential number placed in sealed envelopes and opened only before the commencement of the study. The study was conducted in a single-blind fashion. Patients were followed over the duration of 6 months to assess the reoccurrence of SBP. All the patients were called for examination after every 3 months. At the end of 6th month, efficacy in term of non-reoccurrence of SBP was measured. The data was entered and analyze into statistical packages for social science (SPSS Version 20). Mean ± SD was calculated for age, ChildPugh score, serum creatinine, serum sodium and serum bilirubin. Frequency and Percentage were calculated for gender. Chi-square test was applied to compare the efficacy in both groups by using two-sidedprobability value ≤ 0.05 as statistical criteria of significance. Both groups were compared by age, gender, Child-Pugh score, serum creatinine, serum sodium and serum bilirubin wise stratification by using chi-square test to see the impact of these on outcome variable considertwo-sided probability value ≤ 0.05 as statistical criteria of significance.

RESULTS

In this study 244 patients were divided randomly into two equal groupsto compare the effectiveness of rifaximin versus norfloxacin in prevention of spontaneous bacterial peritonitis in cirrhotic patients. In overall distribution of gender 138 (57%) were male and 106 (43%) were female (Figure 1).

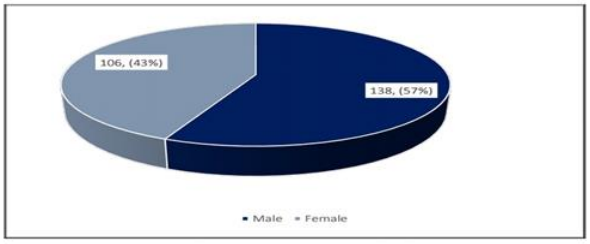

Figure No.1: Overall Distribution of Gender n=244

Table No.1: Distribution of Gender in Both Groups n=244

GROUP	MALE	FEMALE
NORFLOXACIN (n=122)	64 (52.5%)	58 (47.5%)
RIFAXIMIN (n=122)	74 (60.6%)	48 (39.3%)

Table No.2: Comparison of Efficacy in Both Group n=244

GROUP	EFFICACY		P-VALUE
	YES	NO	
NORFLOXACIN (n=122)	103 (84.4%)	19 (15.6%)	0.178
RIFAXIMIN (n=122)	110 (90.2%)	12 (9.8%)	

In group wise distribution of gender 64 (52.5%) male and 58 (47.5%) female was enrolled in norfloxacin group and 74 (60.6%) male and 48 (39.4%) female was included in rifaximin group (Table 2). In comparison of both groups 103(84.4%) efficacy was noted in norfloxacin group whereas 110(90.2%) efficacy was documented in rifaximin group and p value found to be

insignificant i.e.(P=0.178) as shown in Table 2. Stratification of age, gender, serum creatinine, Pugh score, serum sodium, and serum bilirubin with respect to efficacy were done (Table 3-11).

Table No.3: Stratification 0f Age Group 25 To 40 With Respect To Efficacy n=131

GROUP	EFFICACY		P-VALUE
	YES	NO	
NORFLOXACIN (n=61)	49 (37.4%)	12 (9.2%)	0.033
RIFAXIMIN (n=70)	65 (49.6%)	5 (3.8%)	

Table No.4 Stratification 0f Serum Creatinine Group 1.20 – 2.20 With Efficacy n=129

GROUP	EFFICACY		P-VALUE
	YES	NO	
NORFLOXACIN (n=51)	45 (34.9%)	6 (4.7%)	0.859
RIFAXIMIN (n=78)	68 (52.7%)	10 (7.8%)	

Table No.5: Stratification 0f Serum Creatinine Group > 2.20 With Efficacy n=115

GROUP	EFFICACY		P-VALUE
	YES	NO	
NORFLOXACIN (n=71)	58 (50.4%)	13 (11.3%)	0.045
RIFAXIMIN (n=44)	42 (36.5%)	2 (1.7%)	

Table No.6: Stratification of Pugh Score Of 14 – 22 With Efficacy n=161

GROUP	EFFICACY		P-VALUE
	YES	NO	
NORFLOXACIN (n=86)	74 (46.0%)	12 (7.5%)	0.909
RIFAXIMIN (n=75)	65 (40.4%)	10 (6.2%)	

Table No.7: Stratification of Pugh Score > 22 With Efficacy n=83

GROUP	EFFICACY		P-VALUE
	YES	NO	
NORFLOXACIN (n=36)	29 (34.9%)	7 (8.4%)	0.153
RIFAXIMIN (n=47)	45 (54.2%)	2 (2.7%)	

Table No.8: Stratification of Serum Sodium 113 – 124 With Efficacy n=136

GROUP	EFFICACY		P-VALUE
	YES	NO	
NORFLOXACIN (n=72)	63 (46.3%)	9 (6.6%)	1.00
RIFAXIMIN (n=64)	56 (41.2%)	8 (5.9%)	

Table No.9: Stratification of Serum Sodium > 24 With Efficacy n=108

GROUP	EFFICACY		P-VALUE
	YES	NO	
NORFLOXACIN (n=58)	40 (37.0%)	10 (9.3%)	0.050
RIFAXIMIN (n=58)	54 (50.0%)	4 (3.7%)	

Table No.10: Stratification of Serum Bilirubin 0.10 – 2.0 With Efficacy n=70

GROUP	EFFICACY		P-VALUE
	YES	NO	
NORFLOXACIN (n=31)	26 (37.1%)	5 (7.1%)	0.228
RIFAXIMIN (n=39)	37 (52.9%)	2 (2.9%)	

Table No.11: Stratification of Serum Bilirubin > 0.20 With Efficacy n=174

GROUP	EFFICACY		P-VALUE
	YES	NO	
NORFLOXACIN (n=91)	77 (44.3%)	14 (8.0%)	0.524
RIFAXIMIN (n=83)	73 (42.0%)	10 (5.7%)	

DISCUSSION

Transmural bacterial translocation is believed to be a predominant factor in the development of SBP; therefore, prophylaxis is targeted at gut flora [15]. In clinical trials it has been proven that the antibiotic rifaximin has a very good safety profile due to its less absorption from the gut[16, 17]. Few adverse reactions reported were gastrointestinal like flatulence andnausea. Extensive use of norfloxacin has increased the incidence of quinolone resistant and Gram-positive SBP [16].Our study showed that the administration of rifaximin 1200 mg/day in patients with a previous episode of SBP maintained the median count of total white blood cell and neutrophils in ascitic fluid after 3 months of treatment, with no significant difference when compared with those receiving norfloxacin. This was in agreement with Kalambokis et al. [17], who reported significant reductions in white blood cell and neutrophil count in ascitic fluid of cirrhotic patients after a 4-week regimen with rifaximin 1200 mg/day, producing a decrease in SBP frequency and improvement in quality of life in cirrhotic patients with ascites. In the present study, 15.6% on rifaximin and 9.8% on norfloxacin developed SBP during the study period. Our observations are in agreement with the findings of Vlachogiannakos et al. [18], who reported a significantly reduced 5-year probability of SBP in cirrhotic patients taking rifaximin. In the meta-analysis carried out by Bernard et al. [19], comparing several treatments, the general incidence of SBP was 9% in the

norfloxacin-treated group, which was better than our findings in this study. This difference suggests the increased incidence of quinolone-resistant and Gram-positive SBP over the last two decades with extensive and long-term use of norfloxacin for the secondary prophylaxis of SBP. This increased incidence of recurrence of SBP in patients receiving norfloxacin prophylaxis should be watched closely as it suggests reconsidering of the current guidelines for the secondary prophylaxis of SBP. In the current study, the mortality rate was significantly decreased in the rifaximin group (13.74 vs. 24.43%) compared with the norfloxacingroup. Novella et al. [20] compared inpatient and continuous SBP prophylaxis with the norfloxacin group, and mortality rates were 30.2 and 23.2%, respectively, which was similar to our findings. Although there is no current consensus on whether prophylactic antibiotics provide a longterm survival benefit, prophylactic rifaximin was associated with a 30% higher rate of transplant-free survival at 9 months of follow-up in arecent study [21]. In our study, hepatic encephalopathy (HE)-related deaths were threefold higher in the norfloxacin group. A recent study showed that rifaximin at a dosage of 550 mg twice daily was highly effective in decreasing the recurrence of HE and decreasing the rate of HE-related hospitalizations over a 24-week period in a group of patients at high risk for HE [22]. In our study, 84.4% efficacy was noted in norfloxacin whereas 90.2% in rifaximin and p value found to be insignificant. In comparison, our patients who developed SBP during the study duration were significantly more likely to have had a history of previous SBP, higher baseline values for serum bilirubin, prothrombin time and Child–Pugh score. As expected, they also had significantly worse overall survival compared to patients who did not develop SBP. Despite the fact that 15.6% of patients who developed SBP in our study were on rifaximin versus 9.8% on norfloxacin, the difference, however, did not prove to be statistically significant. A few studies have investigated rifaximin versus placebo for SBP prophylaxis in cirrhotics. A cohort study by Terg R, et al. Found a transplant-free survival benefit with the use of rifaximin in cirrhotic patients with ascites and who had no prior history of SBP than those who didn't receive antibiotic prophylaxis [16].Vlachogiannakos et al. Also showed that patients who received rifaximin had a significantly lower risk of developing variceal bleeding, hepaticencephalopathy (HE), SBP and hepatorenal syndrome than matched control subjects who did not receive antibiotic prophylaxis[18]. In comparison, our results demonstrated that patients on rifaximin developed fewer episodes of Hepatic encephalopathy than patients on norfloxacin (4.7% and 9.3%, respectively).Patient succeeded to adhere to therapy slightly better with norfloxacin than rifaximin, and for a significantly longer time. Most patients reported a difficulty to adhere to the three times per day-regimen of rifaximin. The strengths of our study were scientific and systematic calculation of sample size, selection of strongest study design (RCT), and inclusion, exclusion criteria. We also perform stratification at the analysis to control for confounders and effect modifiers. The use of objective definitions for predictor and outcome variable also minimizes the source of bias in our study. There are several limitations to our study. First, since it was impossible to blind the investigator or observer to the device being applied, this study is not a double-blind trial and the potential for bias may exist; this may affect the results as a confounding factor. Also limited outcomes selected in our study affects the worth of our study.

CONCLUSION

As non-significant difference was found between rifaximin versus norfloxacin, so it is to be concluded that rifaximin is as good as norfloxacin. It seems to be an appropriate alternative for long-term primary and secondary prophylaxis of SBP in cirrhotic patients with ascites. There is a need to conduct more randomized studies using large sample size with multiple study centers in Pakistan to confirm the findings of the present study.

Author's Contribution:

Concept & Design of Study:	Aneel Kumar
Drafting:	Bashir Ahmed Shaikh, Zahid Ali Shaikh
Data Analysis:	Aftab Hussain Shah, Arshad Bhutto, Jaipal Das
Revisiting Critically:	Aneel Kumar, Bashir Ahmed Shaikh,
Final Approval of version:	Aneel Kumar

Conflict of Interest: The study has no conflict of interest to declare by any author.

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