Original Article

Comparison of Rifaximin with Norfloxacini in the Primary Prophylaxiso of Spontaneous Bacterial Peritonitis

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Objective: To compare the efficacy of Rifaximin vs Norfloxacin in preventing episode of spontaneous bacterial peritonitis (SBP) in patients with liver cirrhosis.

Methods: It was randomized Controlled Trial conducted at Department of Gastroenterology, Services Hospital, Lahore from 15-09-2015 to 14-03-2016. One hundred patients of both gender in the age range 18-60 with 50 patients in Rifaximin group and 50 patients in Norfloxacin group. Patients after informed consent were randomly assigned to one of the two groups and received prophylaxis for SBP with Rifaximin (1100mg/day) or Norfloxacin (400mg/day) using random tables. Patients were followed up after four weeks and outcome was efficacy in terms of prevention of episode of SBP and was assessed as per operational definition.

Results: A total of 100 patients were included in the study. The mean age of patients was 46.40(± 5.78) years with most of the patients in the age range 31-45 years. Majority of the patients in the study were male (54.0%). Mean polymorphonuclear (PMN) count was 144.4±25.8. Only 7 patients developed SBP, 4 were in Norfloxacin group and 3 were in Rifxaimin group showing efficacy of 92% and 96% respectively with no statistically significant difference(p value >0.05). Stratification of patients by Age, Gender, Duration of disease and Child Pugh score showed p value was >0.05 in all cases showing statistically insignificant difference between various subgroups.

Conclusions: The study shows that rifaximin is as effective as Norfloxacin when used for SBP prophylaxis in cirrhotic patients with ascites.

Keywords: cirrhosis, ascites, spontaneous bacterial peritonitis.

Introduction

The most common bacterial infection in patients with cirrhosis is Spontaneous Bacterial Peritonitis (SBP), ranging from 1030% of all bacterial infections in patients admitted in hospitals.[1] In the nosocomial setting the prevalence is very high ranging from 8% to 36%, however in outpatients without symptoms the prevalence is less than 3.5%.[1] The prevalence of Bacteriascites which is defined as positive culture results but no increase in the leukocyte count in the ascitic fluid is 23% in outpatients with a prevalence of up to 11% in patients admitted in hospitals.[1] The mortality for the first episode of SBP is very high ranging from 10% to 50%[1] during hospital stay. Mortality within first year after an episode of SBP has been reported to be 31% and 93%.[1-2] Bacterial translocation is implicated as the main cause of SBP.[1] Alterations in gut microbiota, increased intestinal permeability and impaired immunity have been implicated in the development of pathological Bacterial Translocation (BT) in liver cirrhosis.[2] SBP is a major complication of ascites and possibly results from a series of events, including intestinal bacterial overgrowth (IBO), BT resulting in bacteremia, endotoxemia, and colonization of mesenteric lymph nodes, and finally seeding of bacteria into the ascitic fluid (AF).[3] The high mortality associated with SBP warrants efforts aimed at prevention with administration of antibiotics to decrease the burden of gut bacteria, thus interrupting the sequence of events leading to ascitic fluid infection. One of the most commonly used medicine for primary prophylaxis of SBP is Norfloxacin; however its extensive long-term use has increased the incidence of quinolone-resistant and gram-positive SBP.[1-2] Overall, the continuous use of a single antibiotic appears not to be the optimal solution and efforts should be made to seek alternatives, which could include antibiotic cycling. The basic principle of cycling antibiotics is that bacteria acquiring resistance to the first course of treatment would remain susceptible to the second regimen, and so on. In this context, Rifaximin holds great promise as it belongs to a different antibiotic class from the antibiotics tested prospectively so far; it exerts a broad range of antimicrobial activity including Gram-positive bacteria; it appears to cause considerably less bacterial resistance.[1-2]

Studies have shown that Rifaximin reduces intestinal bacterial overgrowth, which decreases BT thus

reducing SBP potentially improving survival in cirrhotic patients.[3-6] However, there are certain limitations of available studies. All the studies done so far have used a control group which received no intervention and thus efficacy of Rifaximin cannot be compared to other antibiotics used for the purpose due to difference in patient and study settings.[3-6] In addition, the studies report wide variation in results with Vlachogiannakos J et al. reporting frequency of SBP of 4.5% vs 46% in Rifaximin vs. no antibiotic group while Hanouneh MA found that during the intervention 89% of patients on Rifaximin remained SBP free compared with 68% of those not on Rifaximin.[5,6] Moreover, Lutz P has concluded that Rifaximin does not reduce SBP occurrence in hospitalized patients even though the bacterial species causing SBP were changed by Rifaximin.[7] Fernandez *et al.* showed that Norfloxacin reduced the 1-year probability of SBP from 61% to 7% ($p<0.001$). In another study by Lontos S et al. comparing Norfloxacin with Trimethoprim/Sulfamethoxazole (TMP-SMX), they found 21.6% patients in the Norfloxacin group and 28% in the TMP-SMX group developed SBP ($P > 0.05$).[10] The rationale of present study is that there is no known direct comparison between Rifaximin and Norfloxacin comparing their efficacy in preventing SBP. In addition, there is no study on the subject from Pakistan. Therefore, a study is very much needed to compare the efficacy of Rifaximin and Norfloxacin in preventing SBP as rifaximin exerts a broad range of antimicrobial activity including Gram-positive bacteria and causes considerably less bacterial resistance with significant reduction in episodes of SBP thus improving survival in patients with SBP which carries high mortality rates.[2-4] The aim of our study was to compare the efficacy of Rifaximin vs Norfloxacin in preventing episode of SBP in patients with liver cirrhosis.

Methods

It was quasi experimental randomized controlled trial, conducted in Department of Gastroenterology, Services Hospital, Lahore from: 15-09-2015 to 14-03-2016. Sample size was estimated to be 100 patients with 50 in both Rifaximin and Norfloxacin study arm based with 80% power of test, 5% level of significance and taking and taking expected percentage of efficacy in both groups i.e., 95.5% in Rifaximin group and 78.4% in Norfloxacin group in preventing episode of SBP in patients with liver cirrhosis.[6,10]

We included patients of Liver Cirrhosis of both gender with age ranging between 18 and 60, absence of clinical signs of bacterial infections as per history and examination, no history of variceal bleeding within the 2 weeks preceding the study and no treatment with antibiotics during the last 8 weeks before inclusion.

Patients with previous episode of SBP as per medical record, patients not willing to participate in the study, those with allergy to quinolones, patients of hepatocellular carcinoma or other neoplasia and pregnant and lactating women were excluded.

After taking ethical clearance from hospital ethical committee, 100 patients in total fulfilling the inclusion and exclusion criteria, were included in the study after taking informed consent. Patients were randomly assigned to one of the two groups and received prophylaxis for primary SBP with Rifaximin (1100mg/day) or Norfloxacin (400mg/day) using random tables, Group A received Rifaximin while Group B received Norfloxacin. Bio data was entered in a predesigned structured Proforma. Patients were followed up after four weeks and data entered in the form. Outcome was efficacy in terms of prevention of episode of SBP and was assessed as depending upon whether patients developed SBP or not. Spontaneous Bacterial Peritonitis (SBP) was diagnosed if the polymorphonuclear leukocyte (PMN) cell count in the ascites exceeded 250/µl in a patient with cirrhosis. At 4 weeks, ascites tap was done and fluid was sent to laboratory for analysis for PMN count and efficacy was labelled. Statistical analysis was done using Statistical Package for Social Sciences (SPSS) version 16. Qualitative data like gender, efficacy was presented as frequencies and percentages. Quantitative data i.e., age, leukocyte count etc was presented as means and standard deviations. The efficacy in the two groups was compared by using chi square test. p value less than 0.05 was considered significant. Effect modifiers were dealt with stratifying data for age, gender, and duration of disease, Child Pugh Class which was calculated using the standard method of calculation of Child Pugh Class which includes Presence of Ascites, Hepatic Encephalopathy, Serum Bilirubin, Serum Albumin and International Normalized Ratio. Post stratification chi square test was applied. P value <0.05 was taken statistically significant.

Results

A total of 100 patients were included in the study. The mean age of patients was 46.40 (± 5.78) years and most of the patients were in the age range 46-60 years. Majority of the patients in the study were male (54.0%). Mean PMN count of study participants was

144.4/µl (±25.8). A total of 7 patients out the 100 patients included in the study developed SBP as per the operational definition. Out of 7 patients, 4 were in Norfloxacin group and 3 was in Rifaximin group showing efficacy of 92% and 96% respectively. p value was >0.05 in all 3 cases showing statistically insignificant difference between various subgroups. Out of these 7 patients who developed SBP, between ages 18-30 years, 1 patient was in Rifaximin group while 1 in Norfloxacin group, between ages 31-45 yrs, 1 patient was in Rifaximin group and 2 patients in Norfloxacin group and between ages 46-60 yrs, 1 patient was in Rifaximin group and 1 in Norfloxacin group **(Table-1).** Of these 7 patients, 2 patients were Males in both groups and 1 was female in Rifaximin group and 2 were females in Norfloxacin group. Out of these patients, 1 patient in Rifaximin group and 2 patients in Norfloxacin group had disease duration of 0-5 years, and 2 patients in each group had disease duration of more than 5 years **(Table-2).** On the basis of Child Pugh Score, 1 patient in each group had score of 0-5, 1 patient in Rifaximin group had score of 6-10 while 2 patients in Norfloxacin group had score of 6-10 and 1 patient in each group had score 11-15 **(Table-3)**.

Table-1: Stratification with reference to age of efficacy between both groups (n=100).

Age Group (in years)	Groups	Efficacy		Total	P-value
		Yes	No		
18-30	A	1	5	6	
	B	1	5	6	0.621
	Total	2	10	12	
31-45	A	1	15	16	
	B	2	14	16	0.544
	Total	3	29	32	
46-60	A	1	29	30	
	B	1	25	24	0.918
	Total	2	24	56	

Table-2: Stratification with reference to duration of disease between both groups (n=100)

Duration of Disease	Groups	Efficacy		Total	P-value
		Yes	No		
0-5 years	A	1	22	23	
	B	2	20	22	0.53
	Total	3	42	45	
>5 years	A	2	25	27	
	B	2	26	28	0.970
	Total	4	50	55	

Table-3: Stratification with reference to child pugh score between both groups (n=100).

Child Pugh Score	Groups	Efficacy		Total	P-value
		Yes	No		
0-5	A	1	6	10	
	B	1	7	8	0.867
	Total	2	16	18	
6-10	A	1	14	15	
	B	2	16	18	0.658
	Total	3	30	33	
11-15	A	1	24	25	
	B	1	23	24	0.976
	Total	2	47	49	

Discussion

Rifaximin, a non-absorbable antibiotic, has been licensed for the prevention of relapsing Hepatic Encephalopathy (HE).[7] In addition, due to its broad intestinal antibacterial activity, it is a candidate for the prevention of SBP, which is attributed to intestinal bacterial transmigration.[1] Therefore, we prospectively studied the impact of Rifaximin co-medication on SBP in 100 patients undergoing diagnostic paracentesis in our department. Hanouneh et al. recently reported a retrospective study of 404 cirrhotic patients with HE where rifaximin effectively prevented SBP.[14] However, the authors did not compare Rifaximin to systemic absorbed antibiotic prophylaxis, which is an established clinical standard to prevent recurrent SBP. Furthermore, that study excluded all patients with a high risk for SBP. Another small case control study reported a preventive effect of rifaximin on SBP in a cohort of patients with decompensated cirrhosis.[18] However, that study only included patients who had shown a decrease in the hepatic venous pressure gradient after an initial course of Rifaximin. The authors found a 5-year cumulative survival of 61%. This is remarkable, considering that 5-year mortality in patients with decompensated liver cirrhosis has been reported to be up to 85%.[19] Taken together, these data indicate that there may be a subgroup of cirrhotic patients that benefits from Rifaximin. Rifaximin is a candidate for SBP prevention because it shows broad intestinal antibacterial activity without systemic side effects and because SBP is thought to occur from bacterial translocation. A possible explanation for episodes of SBP during Rifaximin treatment could be resistance to it. This issue is controversial and not easy

To resolve. Some studies reported a slow development and rapid disappearance of resistance to Rifaximin.[7,20,21] In contrast, more recent studies found persistently high rates of resistance in ileal E. coli and in staphylococci.[22-23] The definition of resistance to Rifaximin is difficult, since no data on the intestinal drug concentration are available to define a cut-off for minimal inhibitory concentrations. Fecal levels of Rifaximin are very high but do not necessarily reflect the intra-luminal situation in cirrhotic patients.[24,25] Another recent study did not find any impact of Rifaximin on the development of bacterial resistance in cirrhotic patients.[16] However, this study did not evaluate the effect of Rifaximin on SBP separately.

Given that immune defects are associated with liver cirrhosis and that Rifaximin lacks systemic effects, a general reduction of intestinal bacterial loads by it may suffice to significantly reduce toxin production and to prevent HE, but may not be sufficient for SBP prevention if mucosal translocation of small amounts of bacteria still occurs.[27] This hypothesis is supported by a recent study in cirrhotic patients demonstrating that Rifaximin treatment changed the pattern of metabolites produced by the intestinal bacteria rather than the quantity of bacteria.[29] In our analysis, we compared the efficacy of Rifaximin versus Norfloxacin in preventing episodes of SBP in patients with Liver Cirrhosis. In our analysis, no statistically significant differences were in the rates of SBP between patients receiving SBP prophylaxis with Rifaximin and those treated with Norfloxacin. This suggests that Rifaximin may be as safe and effective as Norfloxacin in the prevention of SBP. This has important implications given the higher cost and concerns about the development of fluoroquinolone resistance when these agents are used for long-term prophylaxis.[9,1113] The overall rates of SBP in both groups in this study were comparable to rates already reported in other studies of SBP prophylaxis. Previous studies have shown SBP prophylaxis to be cost effective when compared to a wait-and-treat approach with the greatest benefit occurring in patients with a previous episode of SBP or low ascitic protein concentration.[15,16] There has been increasing concern about the emergence of fluoroquinolone-resistant organisms in patients who receive prolonged treatment with these drugs.[1,2] Others have found a high rate of fluoroquinolone resistance amongst Gram-negative isolates causing infection.[9] An important additional concern is that a significant proportion of patients on SBP prophylaxis will subsequently go on to liver transplantation and that colonization with Norfloxacin resistant organisms may limit the antibiotic choices available to the treating clinician. Our results suggest that Rifaximin should not generally replace systemically absorbed antibiotics for SBP prophylaxis in patients at high risk for SBP and with recurrent hospitalizations. SBP is a complication of advanced liver disease and our cohort is typical for patients with advanced cirrhosis. However, it remains open whether our findings can be extrapolated to patients at low risk and with less severe liver disease. A further limitation is the fact that we did not measure Rifaximin levels in patient stool to exclude non-adherence with drug therapy. However, the observed clinical improvement of HE suggests good adherence in the studied patient cohort. In addition, the biological intestinal half time of rifaximin is several days and consequently even the omission of one or two dosages would not result in insufficient drug levels.[9,39] Future studies on the effects of rifaximin on SBP should include assessment of bacterial resistance to Rifaximin, which is complicated by the unavailability of commercially available resistance tests or standardized testing procedures with normal values.

Conclusion

In conclusion, this study suggests that Rifaximin is as effective as Norfloxacin when used for SBP prophylaxis in cirrhotic patients with ascites. The increasing concerns about the impact of fluoroquinolone-resistant organisms make this drug an attractive alternative first-line therapy for SBP prophylaxis.

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