THE ROLE OF RIFAXIMINE IN THE PREVENTION OF THE SPONTANEOUS BACTERIAL PERITONITIS

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THE ROLE OF RIFAXIMINE IN THE PREVENTION OF THE SPONTANEOUS BACTERIAL PERITONITIS (Abstract): Cirrhosis is characterized by an increased susceptibility to infection. Spontaneous bacterial peritonitis (SBP) is the most common infectious complication, the main causes being the bowel bacterial overpopulation, the increased intestinal permeability and bacterial translocation. Antibiotic prophylaxis with Norfloxacin increases the rate of PBS with G+ multiresistant bacteria. **Purpose:** to demonstrate the advantage of using rifaximin, nonresorbable broad spectrum antibiotic, in SBP prophylaxis. **Material and methods:** The study is a prospective case-control, which included 46 patients diagnosed with Child class C cirrhosis and refractory ascites, based on clinical, biological, ultrasound and endoscopic findings, followed over a period of 6 months. Protein level in ascitic fluid (AF) was higher 14g/dl. SBP was defined as the presence of > 250 PMN/mm³. Patients were divided into 2 groups, group 1 comprised 22 patients who received rifaximin treatment during the study for a previous episode of hepatic encephalopathy (HE), and group 2 consisted of 24 patients who did not receive antibiotic treatment during follow-up. **Results:** Rifaximin significantly decreases the polymorphonucleares (PMN) in ascitic fluid from patients, one single case of neutroascitic SBP with negative cultures were recorded in this group, with a net improvement of the general condition. In group 2 who did not follow any antibiotic treatment, SBP was recorded in 4 patients, an increase of PMN in ascitic fluid at 14 patients, an approximately constant value in 4 patients, a decrease in 2 subjects. **Conclusions:** The study suggests that rifaximin causes a significant decrease in PMN in AF, producing a decrease in SBP frequency and improvement of life in cirrhotic patients with refractory ascites. In this study, the effects of rifaximin on intestinal bacterial overpopulation and bacterial translocation, decisive factors in SBP, are consistent with literature data. Use of rifaximin as an alternative method to prevent SBP deserves more attention. **Keywords:** SPONTANEOUS BACTERIAL PERITONITIS, BACTERIAL TRANSLOCATION, PROPHYLAXY TREATEMENT, RIFAXIMIN.

Cirrhosis is characterized by an increased susceptibility to infection. In this way, spontaneous bacterial peritonitis (SBP) is a major complication of liver cirrhosis, the incidence in hospitalized patients with ascitic cirrhosis ranging between 7% and 23%, but increased when ascites associated low protein concentration (below 1g/100 ml)
and severe hepatic impairment (1).

In most cases, SBP is a monomicrobial infection, the culture of the ascitic fluid reveals a single microorganism, and the neutrophils being above 250/mm$^3$. The essential pathogenic elements are the intestinal bacterial overpopulation, bacterial translocation, increased intestinal permeability and immune deficiency.

Translocation of bacteria is defined as the passage of viable bacteria from the gastrointestinal tract to extra-intestinal sites, such as mesenteric lymph nodes (MLN), liver, spleen, kidneys, and blood flow. Overgrowth of the intestinal gram-negative bacilli will be followed by translocation in mesenteric lymph nodes, in the conditions of disruption of the intestinal barrier (2). Unlike the aerobic bacteria, which translocate through an intact mucosa, the anaerobic bacteria translocate through an intestinal mucosa defect (3). In fact, by eliminating the anaerobic bacteria, the intestinal bacterial overgrowth is facilitated, which one of the main factors is promoting bacterial translocation (4).

The long term prognosis of patients with SBP is unfavorable, the recurrence rate being 43% at 6 months. Despite the use of empirical antibiotic therapy, particularly cefotaxime, as well as antibiotic prophylaxis, currently mortality ranges from 10-30% (5).

A recent study shows that 30.8% of patients with Child class C cirrhosis, who did not have antibiotic treatment, have enteric bacteria in the mesenteric lymph nodes, while only 4.5% of those who were treated for decontamination have an enteric bacterial population in the mesenteric lymph nodes (6). Induced antisecretory hypochlorhydria favors the intestinal bacterial overgrowth. In patients with liver cirrhosis there is an intestinal motility disorder, which promotes intestinal bacterial overpopulation.

An important problem which has been recently discussed is the prophylactic treatment of spontaneous bacterial peritonitis with Norfloxacin (400 mg orally every 12 hrs.) considering the possibility to select quinolone-resistant bacteria species. However, special attention and a high degree of suspicion should be maintained in patients with spontaneous bacterial peritonitis that followed the prophylactic treatment. If the standard treatment fails, a 48h control paracentesis should be associated with vancomycin and imipenem (7).

Since 1994, investigators have explored the possibility of resistant bacteria species in patients receiving norfloxacin 400 mg daily to prevent SBP (8). By observing quantitative stool cultures of 31 patients, no resistant organisms were isolated from 15 patients, however, fluoroquinolone-resistant organisms were isolated from 16 patients between days 14 and 43, inclusive Staphylococcus spp aureus coagulase-negative, Citrobacter freundii, Enterobacter cloacae, Klebsiella oxytoca, and Proteus rettgeri.

In this way, considering that antibiotic prophylaxis of SBP with Norfloxacin increases the G+ multiresistant bacteria, the aim of the present work was to prove the advantage of using rifaximin, non-resorbable broad-spectrum antibiotic in SBP prophylaxis.

**MATERIAL AND METHODS**

The study is a prospective case-control, which included 46 patients diagnosed with Child class C cirrhosis and refractory ascites, based on clinical, biological, ultrasound and endoscopic findings, followed
The role of rifaximine in the prevention of the spontaneous bacterial peritonitis

over a period of 6 months. Patients were divided into 2 groups, group 1 comprised 22 patients who received rifaximin treatment during the study for a previous episode of hepatic encephalopathy, and group 2 consisted of 24 patients who did not receive antibiotic treatment during follow-up. Protein level in AF was higher than 1.4 g/dl. SBP was defined as the presence of > 250 PMN/mm³. Diagnostic paracentesis was done with white blood cells (WBC) and PMN counting, and biochemical determinations (proteins, glucose). Cultures of the AF have also been done.

Our data were statistically analyzed by using one-way analysis of variance (ANOVA). All results are expressed as mean ± SEM. F values for which p<0.05 were regarded as statistically significant.

RESULTS

Regarding the distribution of the PMN values, as a result rifaximin administration for 6 months, we could observe that a high percentage of the treated patients manifested a decrease in their levels of PMN (20 patients out of 22 ~ 90 %). Also, only one case each, for stable PMN and SBP (5 %) is reported for this group (fig. 1).

When analyzing the changes observed after 6 months in the untreated group, we observed that most of the patients (58 %) experienced an increase in their levels of PMN, with only 8 % of them having decreased number of PMN and 17 % each for stable values of their PMN or SBP (fig. 2).

Fig. 1. The percentage distribution of the PMN values, after 6 months of rifaximin administration

Fig. 2. The percentage distribution of the PMN values, after 6 months, in the untreated patients
Table I presents the detailed average values for the PMN levels at the baseline point, as well as after 6 months, in both our study groups (treated vs. untreated) (tab. I). We could observe a significant difference (\(F(1.42)=6, p=0.022\)) between the baseline point and after 6 months of treatment in our group of patients treated with rifaximin. Conversely, there were no significant differences (\(F(1.46)=1, p=0.066\)) between baseline levels and after 6 months levels in the group of untreated patients, as shown by ANOVAs One Way (tab. I).

**TABLE I**

The PMN values, at the baseline point and after 6 months, in treated and untreated patients

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<tr>
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<th>Treated</th>
<th>Untreated</th>
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<tr>
<td></td>
<td>Baseline (\bar{x}) ± SD</td>
<td>6 months (\bar{x}) ± SD</td>
</tr>
<tr>
<td>PMN</td>
<td>101.09 ± 8.67</td>
<td>62.5 ± 13.82</td>
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Moreover, our final analysis focused on the possible differences between groups of patients after 6 months (treated vs. untreated). As can be seen in the Figure 3, we observed an increase of the PMN values in the untreated group, when compared with patients treated with rifaximin (\(F(1.44) =3, p=0.1\)) (fig. 3).

**DISCUSSION**

The present study demonstrated that rifaximin is associated with a significant decrease of PMN in the ascitic fluid, which could suggest that it could be implicated in the decrease of SBP frequency, and also in improving the quality of life in cirrhotic patients with refractory ascites.

These aspects could be very important considering that rifaximin, nonresorbable broad-spectrum antibiotic, has less adverse effects and does not increases the G+ multiresistant bacteria.

Cirrhotic patients have frequent episodes of infections due to immunodeficiency and malnutrition, which justifies prophylactic antibiotic treatment. Establishing the optimal therapeutic dose should
avoid the selection of multiresistant bacteria (9).

Among hospitalized patients, it was found that 16% had a multidrug-resistant bacteria, (most often Staphylococcus), mostly those who received prior antibiotic treatment. Germs are often 10 times more aggressive in 33% of cases, resulting a longer hospitalization period and also increased hospital mortality (10).

A direct relationship between micro biota composition and bacterial translocation was demonstrated in mice. Bacterial overgrowth that occurs in cirrhosis due also to the intestinal hipomotility was correlated with bacterial translocation, endotoxemia and the development of spontaneous bacterial peritonitis (11).

Authors warned against antibiotic prophylaxis in patients with cirrhosis. Subsequent studies have shown changes in the epidemiology etiology associated with PBS antibiotic prophylaxis (11).

In consideration of two time periods (1991-1995 and 1996-2000), Singh et al. have shown that the incidence of SBP with multidrug-resistant organisms in patients who were admitted in a liver transplant unit increased from 8.3% to 38.5%, the most resistant pathogens (71%) were either ESBL-producing organisms and methicillin-resistant S. aureus. The researchers noted that asymptomatic colonization of the gastrointestinal tract with ESBL-producing organisms normally precedes the symptoms. With the occurrence of gram-positive methicillin-resistant (MRSA) and gram-negative ESBL-producing germs, it seems prudent to evaluate patients with resistant pathogens SBP. (12). Thus, if patients who have received prior fluoroquinolones as SBP prophylaxy do not respond to empiric treatment after 48 hours, vancomycin (Vancocin, Viro Pharma) should be added to the treatment. Local epidemiological results also support the transition to antibiotics such as ertapenem (Invanz) or tigecycline (Tigacil). (12, 13).

In a recent study, it was demonstrated that in the cirrhotic patients which were not treated with fluoroquinolone, the dominant spectrum in the ascitic fluid is represented by gram-negative bacteria (67%), whereas in those treated the dominate germs were gram positive bacteria. (14)

Given the increased cost and risk of developing resistant organisms, antibiotic prophylaxis is indicated in the following three groups: the history of SBP, those hospitalized for upper gastrointestinal bleeding and those with low-protein-concentration in AF.

Selective decontamination by prophylactic antibiotic aims to reduce the bacteria from the gastrointestinal tract in order to reduce the risk of developing spontaneous bacterial peritonitis.

Also, a recent study by Kalambokis et al. (15) demonstrated that administration of a therapy for four weeks with rifaximin 1.200 mg / day significantly reduced the number of neutrophils in the ascites fluid of cirrhotic patients with sterile ascites, in accordance with a significant decrease in plasma endotoxin. The observations are consistent with recent findings that show a significantly reduced rate in developing SBP after 5 years in cirrhotic patients receiving rifaximin.

**CONCLUSIONS**

The present study suggests that rifaximin cause a significant decrease in PMN in AF, causing a decrease in SBP frequency and improvement of life in cirrhotic patients with refractory ascites. In this study,
the effects of rifaximin on intestinal bacterial overpopulation and bacterial translocation as decisive factors in SBP, are consistent with literature data. Therefore the use of rifaximin as an alternative method to prevent SBP deserves more attention.

REFERENCES