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Role of Rifaximin and Zinc in Secondary Prevention of Spontaneous Bacterial Peritonitis in Cirrhotic Patients

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Abstract: Spontaneous bacterial peritonitis (SBP) is a frequent fatal complication in patients with liver cirrhosis with ascites that is characterized by recurrence. Rifaximin is a poorly absorbable antibiotic with a broad spectrum antibacterial action and has low risk of introducing bacterial resistance. Zinc is a very important trace element in protection against infections although it is deficient in most of the cirrhotic patients. The current study aimed at evaluation of the efficacy of administration of oral rifaximin with or without zinc in the secondary prevention of SBP in Child C Egyptian cirrhotic patients. The study was conducted on sixty cirrhotic patients presenting with SBP who had received a full dose of treatment by cefotaxime 2gm IV and after complete cure of the attack of SBP patients were divided into 3 groups who were followed up during a period of 4 months for the recurrence of SBP, group I; 20 patients received 1200 mg rifaximin and 150 mg zinc daily for 4 months.groupII;20 patients received only 1200 mg of rifaximin daily for the same 4 months and group III:20 patients did not receive any prophylactic medication (control group) .In our study, after receiving full dose of rifaximin for 4 months PMN cell count remained stable less than 250 cells in 75% of the patients and decreased in 10% of the patients thus prevent the recurrence of SBP in 85% of the patients. Patients also showed improvement in clinical signs and symptoms, so that there was 55% improvement in abdominal pain 45% improvement in hepatic encephalopathy and fever. In comparison with the control group regarding to the PMN cell count15% of the patients had stable high results, 15% had fluctuating results and 15% had increased results so recurrence rate increased by 45% during 4 months after the attack of SBP. There was no significance between group I and group II (prophylaxis groups), so zinc had no significant value. Conclusion: rifaximin was effective antibiotic in secondary prevention of SBP, but zinc showed no efficacy in secondary prevention of SBP.

Key words: Liver cirrhosis · Spontaneous bacterial peritonitis · Rifaximin

INTRODUCTION

Spontaneous bacterial peritonitis is a frequent complication in patients with liver cirrhosis with ascites and is associated with a significant morbidity and mortality rate that approaches 100% if untreated [1]. Cefotaxime has been the most extensively studied antibiotic for this infection. It was considered to be one of the first choices because of its low toxicity and excellent efficacy [2]. The appreciation of the potential role of enteric flora in the pathogenesis of several gastrointestinal diseases has broadened the clinical use of rifaximin, which is now used for hepatic encephalopathy [3]. Theoretically, by reducing the total number of the gut bacteria, rifaximin could also be used to achieve intestinal decontamination in patients with liver cirrhosis and ascites, thus preventing SBP(Spontaneous bacterial peritonitis). Zinc which is a trace element plays an essential role in numerous biochemical pathways. It affects many organ systems, including the skin, gastrointestinal tract, central nervous system, skeletal, reproductive and immune systems [4].

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The current study aimed at evaluation of the efficacy of administration of oral rifaximin with or without zinc in the secondary prevention of SBP in Child C Egyptian cirrhotic patients.

MATERIALS AND METHODS

In the period between March 2016 and August 2016, patients with liver cirrhosis and ascites and clinical findings suspicious of ascitic fluid infection who were admitted to the liver unit at Theodor Bilharz institute were enrolled in this study after signing written informed consent and after proving the diagnosis of SBP by diagnostic paracentesis, they received the appropriate treatment.

Sixty Child C Cirrhotic Patients: Were diagnosed as (SBP) by clinical, laboratory and histopathological examination, they were divided into 3 groups:

Group I, 20 patients received 1200 mg rifaximin and 150 mg zinc daily for 4 months.

Group II, 20 patients received only 1200 mg of rifaximin daily for the same 4 months.

Group III, 20 patients did not receive any prophylactic medication.

So, group I and II were the prophylaxis groups and group III was the control group.

Exclusion Criteria:

- Patient presented with secondary bacterial peritonitis, which is infection of the ascitic fluid by multiple organisms mainly it was a post -operative complication.
- Patients who received antibiotics other than rifaximin for prevention of SBP.
- Patients who received prophylactic antibiotic for any medical indication
- Patient who received supplemental treatment of zinc or containing zinc. .
- Cirrhotic Patients who presented with hepatocellular carcinoma.

The patients in all groups were subjected to the following after signing informed consent for joining the study;

- Thorough medical history with stress on symptoms of SBP as abdominal distention with abdominal pain, fever, lethargy, disturbed sleep rhythm and decreased urinary output.
- Clinical examination with stress on:

- Guarding
- Abdominal tenderness
- Shifting dullness
- Investigations

Laboratory

- *Complete blood count*
- *Renal functions* :urea, creatinine
- *Liver functions:* ALT, AST, S. bilirubin, S.albumin
- *Electrolytes*; sodium and potassium
- *Prothrombin concentration*; INR
- *Serum zinc level*: basal serum zinc was measured in all of the sixty patients, but only it was followed up in twenty patients in group I after receiving full dose for 4 months.
- *Examination of the ascitic fluid*: Ascitic fluid samples were aspirated on the day of admission under complete aseptic conditions in tubes.

The aspirated samples were checked for:

- White blood cell (WBC) and polymorphonuclear leucocytes (PMN) counts done by automated system (SYSMEX cell counter).All the specimens were analyzed within one hour.
- Biochemical assay of total proteins, glucose, LDH levels, ascitic fluid albumin and Serum Ascites Albumin Gradient (SAAG). Calculating SAAG involves measuring the albumin concentration of serum and ascitic fluid specimens obtained on the same day and subtracting the ascitic fluid value from the serum value.
- Blood culture bottle: using aerobic and anaerobic BacT/AL blood culture bottles which were inoculated with 10ml of ascitic fluid at the bedside [5] and then placed in the BacT/ALERT instrument for bacteriological examination. Bacterial identification and antimicrobial susceptibility testing were carried out by microscopy (automated biochemical reactions)(6).

Imaging;

- *Abdominal imaging*

Treatment: With Cefotaxime, as empirical treatment with maximum dose 2gm IV, every 8 hours starting just after taking the ascitic fluid sample for 5days.The antibiotic dosage was adjusted to the renal function throughout the treatment period(7).

Follow up: After complete cure of the current attack of SBP which was evidenced clinically and laboratory.

The 3 groups of patients were followed up as the following;

They were all subjected monthly to full routinely clinical examination, Clinical signs and symptoms of infection (fever, abdominal pain, mental status change, hypotension, etc) were recorded and white cell count and PMN counts in ascitic fluid were also performed .

Prophylactic treatment failure was established when the condition of the patients rapidly deteriorated during the monthly visits, or when there was increase in number of neutrophil count above 250 cells/mm³in the follow-up paracentesis.

Prophylactic treatment success was established when all the clinical signs of infection were not present, the PMN cell count in the ascitic fluid was decreased to less than 250 cells/mm³, total and differential WBC counts were normalized and blood and ascitic fluid cultures were negative.

Statistical Analysis: It was done by using software package (SPSS PC, Chicago, IL) version 18.The difference between groups (More than 3 groups) were analyzed for statistical significance by one way ANOVA test. All tests were two tailed considered statistically significant when p value < 0.05.

RESULTS

The 3 groups were age and sex matched, the age distribution ranged from 51years to 65 years (mean 58.67±6.8) including 40 males (66.7%) and 20 females (33.3%).

Regarding the clinical manifestations of the patients, there was no significant difference between the three groups regarding; abdominal pain and tenderness were found to be the most prevailing clinical manifestation around 73.3%.

Also, around 63.3% of patients had history of hepatic encephalopathy and 45% of the patients had history of bleeding. Around 41.7% of the patients presented to us with fever.

All of the patients were anemic with mean hemoglobin was (9.24± 1.82gm/L), Most of the patients presented with hyperbilirubinemia with mean total bilirubin (3.6 ± 3.09mg/dl), hypoalbuminemia with mean albumin (2.36 ± 0.46 gm/dl) and elevated liver enzymes with mean AST (93.12± 114.01IU/L) and mean ALT (41.25±32.09 IU/L) .

Most of the patients showed coagulopathy with mean INR was (1.89± 0.69) and mean prothrombin concentration (54.89±19.93 %). Most of them presented with renal impairment with mean creatinine was (1.77± 1.3mg/dl) and hyponatremia with mean serum sodium was (129.45± 8.49mmol/l). Most of patients showed zinc deficiency with mean serum zinc was 55.5 in all groups at the time of admission, but it was increased in group one after administration of150 mg daily oral zinc for 4 months, mean zinc after (117.50±22.109) so this dose was sufficient to treat zinc deficiency. By using the BacT/ALERT culture system E. coli was found to be the most common organism in 60% of the patients.

After four months of prophylaxis clinical data were followed up and analyzed:

It was found that, after the intake of rifaximin and zinc in group I and intake of rifaximin only in group II around 45% of the patients in both groups resolved from hepatic encephalopathy while only 5% of the patients had recurrent attacks of HE. In group 3 around 35% of the patients improved from hepatic encephalopathy and about 25% of patients worsen. There was no significance between group I&II so zinc has no added value. In group I&II 45% of the patients improved from fever and 25% got recent fever while in group III, 20% of the patients improved and 35 %got recent fever. There wasn't any significance between group I&II so zinc has no added value.

Also in group I and II around 55% of the patients improved from abdominal pain and tenderness. While in group III only 45% of patients improved from abdominal pain and tenderness, there was also no statistical significance between group I and II so, zinc has no added value.

After four months of prophylaxis change in neutrophil count was followed up and analyzed:

There was no significance between the three groups during the first 2 months of follow up, other wise In third month of follow up, 11 patients presented with neutrophil count more than 250, three patients from group I(15%), two patients from group II (10%) and six patients from group III (30%) and In the fourth month of follow up,

Table 1: Bacteriological Analysis of Ascetic Fluid

		Groups			
		Group I	Group II	Group III	Total
Citrobact	Count	3	2	2	7
R	%	15.0%	10.0%	10.0%	11.7%
E. coli	Count	13	10	13	36
	%	65.0%	50.0%	65.0%	60.0%
Enteroc	Count	0	1	1	2
	%	.0%	5.0%	5.0%	3.3%
KL SPP	Count	1	1	2	4
	%	5.0%	5.0%	10.0%	6.7%
PROT SPP	Count	1	0	1	2
	%	5.0%	.0%	5.0%	3.3%
STAP	Count	0	1	1	2
Coag+	%	.0%	5.0%	5.0%	3.3%
Staph coag -v	Count	2	5	0	7
	%	10.0%	25.0%	.0%	11.7%
Total	Count	20	20	20	60

Table 2: The antibiotics sensitivity pattern for each isolated organism

Species	Amikacin	Imipenem	Cefotaxime	Chloramphenicol	Cefoperazone sulbactam	Meropenem	Ciprofloxacin	Vancomycin	Cefoperazone
Escherichia coli (No=32)	24 (75%)	18(56.2%)	10 (31.2%)	10 (31.2%)	5 (10%)	5 (10%)	7 (14%)	2 (6.25%)	2(6.25%)
Citrobacter (No=6)	4(66.6%)	2 (33.3%)	1 (16.6%)	2 (33.3%)	1(16.6%)	1 (16.6%)	1 (16.6%)	1(16.6%)	1(16.6%)
Klebsiella (No=1)	1(100%)	0 (0%)	1 (100%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Proteus(No=1)	1(100%)	0 (0%)	1 (100%)	0 (0%)	0 (0%)	0 (0%)	1 (100%)	0 (0%)	0 (0%)
Staph- coagulase negative (No=8)	5(62.5%)	1(12.5%)	3 (37.5%)	3 (37.5%)	1(12.5%)	1(12.5%)	1(12.5%)	5(62.5%)	5 (62.5%)
Enterococci (No=1)	0 (0%)	0 (0%)	1 (100%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	1 (100%)	1 (100%)
Staph-coagulase positive (No=1)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	1 (100%)	0 (0%)

Table 3: Pattern of change in neutrophil count among the studied groups

			Groups				
			Group I	Group II	Group III	Total	P value
Pattern count	Stable <250	Count	15	14	11	40	<0.01 (S)
		%	75.0%	70.0%	55%	66.6%	
	Decrease	Count	1	3	0	4	
		%	5.0%	15.0%	0%	6.6%	
	Fluctuating	Count	3	2	3	8	
		%	15.0%	10.0%	15.0%	13.3%	
	Increase	Count	1	1	3	5	
		%	5.0%	5.0%	15.0%	8.3%	
	Stable high	Count	0	0	3	3	
		%	.0%	.0%	15.0%	5%	
	Total	Count	20	20	20	60	
		%	100.0%	100.0%	100.0%	100.0%	

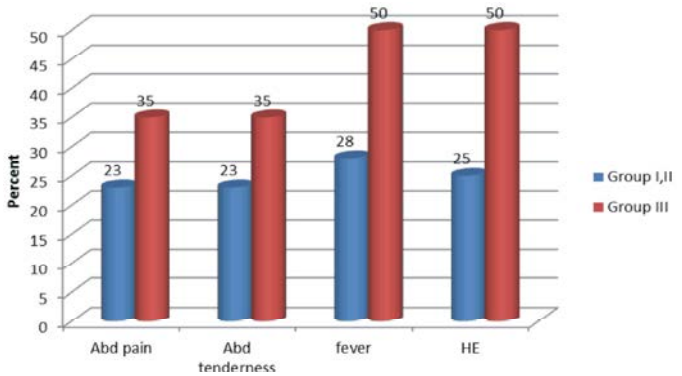

Fig. 1: Signs and symptoms follow up of groups I&II vs. Group III.

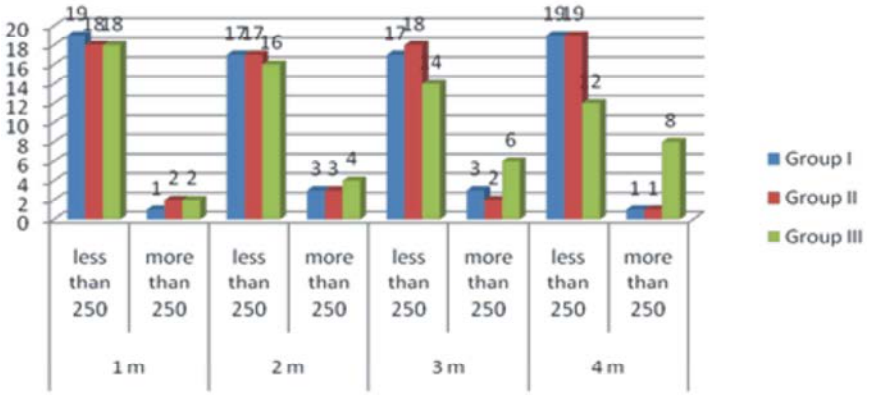

Fig. 2: Pattern of neutrophil count during the period of Follow up

10 patients presented with neutrophil count more than 250, only one patient from group 1 (5%), 1 patient from group 2 (5%) and 8 patients from group 3(40%). so in group III recurrence of disease increased during third and fourth months without any prophylaxis but in the other two groups by the fourth month with full dose of rifaximin in group2 and rifaximin and zinc in group 1 recurrence was decreased. During the four months of prophylaxsis in group I&II around 72% of patients had a stable neutrophil count less than 250 cells, 10 % of patients had decreased neutrophilic count, 13% of patients had a fluctuating results and 5 % of patients had increase in neutrophilic count. While, in group III 3, 5 % of patients had a stable neutrophil count less than 250 cells, 15% of patients had fluctuating results and 15% of patients experienced increased neutrophil count and 15% had a stable high results from the beginning with no decrease in neutrophil count.

There was no significance between group I and II regarding change in neutrophilic counts, so zinc had no significant value.

DISCUSSION

Spontaneous bacterial peritonitis is a frequent complication in patients with liver cirrhosis with ascites and is associated with a significant morbidity and mortality rate that approaches 100% if untreated [1]. Rifaximin is an antibiotic which is active against a variety of aerobic and anaerobic Gram-positive and Gram-negative organisms, as well as protozoal infections [8]. The appreciation of the potential role of enteric flora in the pathogenesis of several gastrointestinal diseases has broadened the clinical use of rifaximin, which is now used for hepatic encephalopathy [3]. Theoretically, by reducing the total number of the gut bacteria, rifaximin could also be used to achieve intestinal decontamination in patients with liver cirrhosis and ascites, thus preventing SBP. This study was conducted to assess the effectiveness of using rifaximin alone versus rifaximin and zinc in preventing the recurrence of SBP in cirrhotic patients after cure of current attack of SBP.

In the present study, age of patients ranged from 51 years to 65 years (mean 58.67 ±6.8). The number of males (66.7%) was significantly higher than females (33.3%) and this agrees with a study conducted by Hanouneh *et al*. [9] who studied 404 patients, the mean age of the enrolled patients was 54.3±9.7 years, with 143 female patients (35.4%) and 261 male patients (64.6%).

Regarding the clinical manifestations of the studied patients, the most common clinical finding was abdominal tenderness (73.3%); this coincides with Webster *et al*. [10] who stated that the most significant clinical signs for SBP were abdominal tenderness.

Regarding the organisms isolated, Escherichia coli was isolated in 36 patients (60%), staphylococcus coagulase negative in 7 patients (11.7%), Citrobacter in 7 patients (11.7%), Klebsiella in 4 patients (6.7%), Proteus in 2 patients (3.3%), Enterococci in 2 patients (3.3%), staphylococcus coagulase positive in 2 patients (3.3 %) and no anaerobic organisms were detected.

Cefotaxime has been the most extensively studied antibiotic for this infection. It is considered to be one of the first choices because of low toxicity and excellent efficacy [2]. In our study, after intake of rifaximin and zinc in group I and intake of rifaximin only in group II for four months, the 3 groups of patients clinical data and ascitic fluid cell count were analyzed, 55%of patients with ascitic fluid infection improved from their tenderness and rebound tenderness in group I &II while 35% of patients in group III which showed no statistical significance between the prophylaxis groups and the control

group.45% of patients showed improvement in fever in groups I &II while only 20% in group III and 45% of patients showed improvement in hepatic encephalopathy in group I &II while 35% in group III which showed statistical significance between prophylaxis groups and control group, this result coincides with the study of philipplutz *et al*. [11]. Regarding PMN cell count after 4 months of prophylaxsis, PMN cell count was <250 cells/mm^3 in 72 % to 75% in the prophylaxis groups while 55% in the control group, PMN cell count was increasing in only 5% of patients in the prophylaxis groups while in 15% in the control group, it also was fluctuating in 13% in patients in the prophylaxis groups while in 15% in the control group. There was decrease in PMN cell count in 10% of patients in the prophylaxis group while there was no decrease in number of PMN cell count in the control group and 15% in the control group the PMN cell count were stable high, So there were statistically significant difference between the prophylaxis and control groups regarding change in PMN cell count and this was is in agreement with a study done by Dãnulescu *et al*. [12] which stated that a high percentage of the treated patients with rifaximin showed a decrease in their levels of PMN; 20 patients out of 22 (90 %) and the other two cases, first showed stable PMN and the other manifested by SBP (5 %). In our study 85% of the patients in the prophlaxis group had experienced improvement of PMN cell count less than 250 cells (same result at discharge)while 15% of those patients worsened and 55% of the patients in the control group had experienced improvement of PMN cell count less than 250 cells (same result at discharge) while 45% of those patients worsened this also coincides with the study of Dãnulescu *et al*. [12] which stated that 90% of the patients on rifaximin showed improved PMN cell count less than 250 while only 25% of the patients on no treatment showed improved PMN cell count less than 250 and also coinciding with the study of Hanouneh *et al*. [9] which stated that there was 72% decrease of the risk of development of SBP in patients who are treated with rifaximin compared to the untreated patients. Our study disagrees with the study of Parcina *et al*. [11] who stated that rifaximin should not generally replace systemically absorbed antibiotics for SBP prophylaxis in patients at high risk for SBP and with recurrent hospitalizations.

Zinc deficiency/altered metabolism is observed in many types of liver disease, including alcoholic liver disease and viral liver disease. Some of the mechanisms for zinc deficiency/altered metabolism include decreased dietary intake, increased urinary excretion, activation of certain zinc transporters and induction of hepatic metallothione[13].Impaired immune function in people with zinc deficiency can lead to the development of respiratory, gastrointestinal, or other infections, e.g., pneumonia and may lead to spontaneous bacterial peritonitis. Zinc had no role in our study in prevention of SBP as an infection in cirrhotic patients in which group one had received 50 mg zinc orally 3 times daily for 4 months.

CONCLUSIONS

In Conclusions, Rifaximin is effective antibiotic in secondary prevention of SBP, but zinc showed no efficacy in secondary prevention of SBP.

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