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Norfloxacin with itopride versus norfloxacin alone in secondary prophylaxis of spontaneous bacterial peritonitis: a randomized trial

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Abstract

Background: Bacterial translocation is considered the pathophysiological hallmark in the development of spontaneous bacterial peritonitis (SBP). Prokinetics can increase gastrointestinal (GIT) motility, reduce small bowel transit time, decrease bacterial translocation, and the possibility of SBP. The aim of this work was to compare the effectiveness and safety of itopride and norfloxacin versus norfloxacin only in secondary prophylaxis for cirrhotic ascitic patients with spontaneous bacterial peritonitis.

Results: Regarding the baseline clinical manifestations and laboratory investigations, there was no significant difference between both groups. The incidence of a recurrent SBP in group I, who had received itopride plus norfloxacin, reduced with a significant difference than other group II ($P=0.018$). The median time for recurrence of SBP was highly longer in group I than group II with a significant difference ($P=0.042$).

Conclusions: The combined usage of itopride with norfloxacin in patients with cirrhosis and ascites can decrease the occurrence of a recurrent SBP and significantly improve the survival of patients.

Trial registration: ClinicalTrials.gov Identifier: [NCT04161768](https://clinicaltrials.gov/ct2/show/study/NCT04161768).

Keywords: Spontaneous bacterial peritonitis, Cirrhosis, Ascites, Prokinetics, Norfloxacin, Itopride

Background

Spontaneous bacterial peritonitis (SBP) is an ascitic fluid infection that occurs spontaneously with no overt source that can be remedied surgically. It is a common complication in cirrhotic patients with ascites. All cirrhotic patients with ascites are at risk of SBP. The occurrence of SBP is 1.5–3.5% in outpatients and is about 10% in hospitalized patients [1].

The most common life-threatening complication in patients with cirrhosis and ascites is SBP and the mortality rate ranges between 30 and 50%; prompt diagnosis

and treatment are the most common variable causes in reducing morbidity and mortality from SBP [2].

When the number of polymorph nuclear cells was >250 cells/mm³ in ascitic fluid in the absence of the source of intra-abdominal infection, the diagnosis of SBP is established [1].

Variable factors are associated with the development of SBP but bacterial translocation is considered the pathophysiological hallmark in immune-compromised hosts in the pathogenesis of SBP [3].

SBP treatment is based on the administration of broad-spectrum empiric antibiotics such as third-generation cephalosporins. For patients with beta-lactam allergy, alternatives include fluoroquinolones such as levofloxacin can be administered [4].

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Recently, it was found that prokinetics could increase GIT motility, decrease small bowel transit time and decrease small intestinal bacterial overgrowth (SIBO), so could decrease bacterial translocation and the possibility of SBP [5].

The aim of the work was to compare the effectiveness and the safety of itopride with norfloxacin versus norfloxacin only in secondary prevention of spontaneous bacterial peritonitis in cirrhotic ascitic patients.

Methods

This randomized study was conducted on 80 cirrhotic patients with ascites and previous episode of SBP attending to the Tropical Medicine Department of Tanta University Hospital in a time of 1 year since December 2018 toward December 2019. The committee of ethics of scientific research of Tanta Faculty of Medicine approved the studied protocol and written consents were obtained from the studied groups for participation. The study was registered on clinicaltrials.gov with a registration number NCT04161768. For comparing the 2 groups, we adopted simple randomization through computer-generated random numbers with equal allocation ratio by referring to a table of random numbers.

Patients with cirrhosis and ascites and with previous events of SBP who were diagnosed by pelvi-abdominal ultrasound, liver function tests, and ascitic fluid aspiration, and analysis were included in the study and all patients included in our study did not receive prokinetics before. However, patients with ascites due to causes other than cirrhosis, patients with hepatocellular carcinoma or any other neoplastic disorder, pregnant and lactating women, patients with recent antibiotic therapy in the 2 weeks before or patients with allergy or other contraindications of the used drugs were excluded from the study.

Patients in our study were randomized into 2 groups: group 1, cases who received itopride 150 mg daily plus norfloxacin 400 mg daily; group 2, patients who received norfloxacin 400 mg daily alone. The two studied groups were followed up for 6 months, every 2 months for ascitic fluid analysis and when the clinical examination can be suggested SBP signs such as fever, tenderness, abdominal pain, or vomiting are present. The compliance was detected by asking the patients through their telephone numbers and by recovery of empty drug envelopes. Flow chart of the study is demonstrated in Fig. 1.

All patients were subjected for full history taking with attention on history of a previous attack of SBP, symptoms related to spontaneous bacterial peritonitis, history of treatment received through the 2 weeks before ascitic sample aspiration or history of the hepatic encephalopathy. Complete physical examination with attention on manifestations of advanced chronic liver disease.

Laboratory investigations was performed for all the patients enrolled in the study including complete blood count (CBC), liver biochemical investigations, coagulation profile, kidney function assessments, serum C-reactive protein (CRP), ascitic fluid chemical, physical and cytological analysis and culture, and the serum-ascites albumin gradient (SAAG). Pelvi-abdominal ultrasound was done for all patients to assess liver conditions and aspiration of ascitic fluid sample can be performed.

The primary end point was the percentage of patients who developed a recurrent attack of SBP at the end of six months follow up. The secondary end points were the mortality rate in both groups.

Statistical analysis

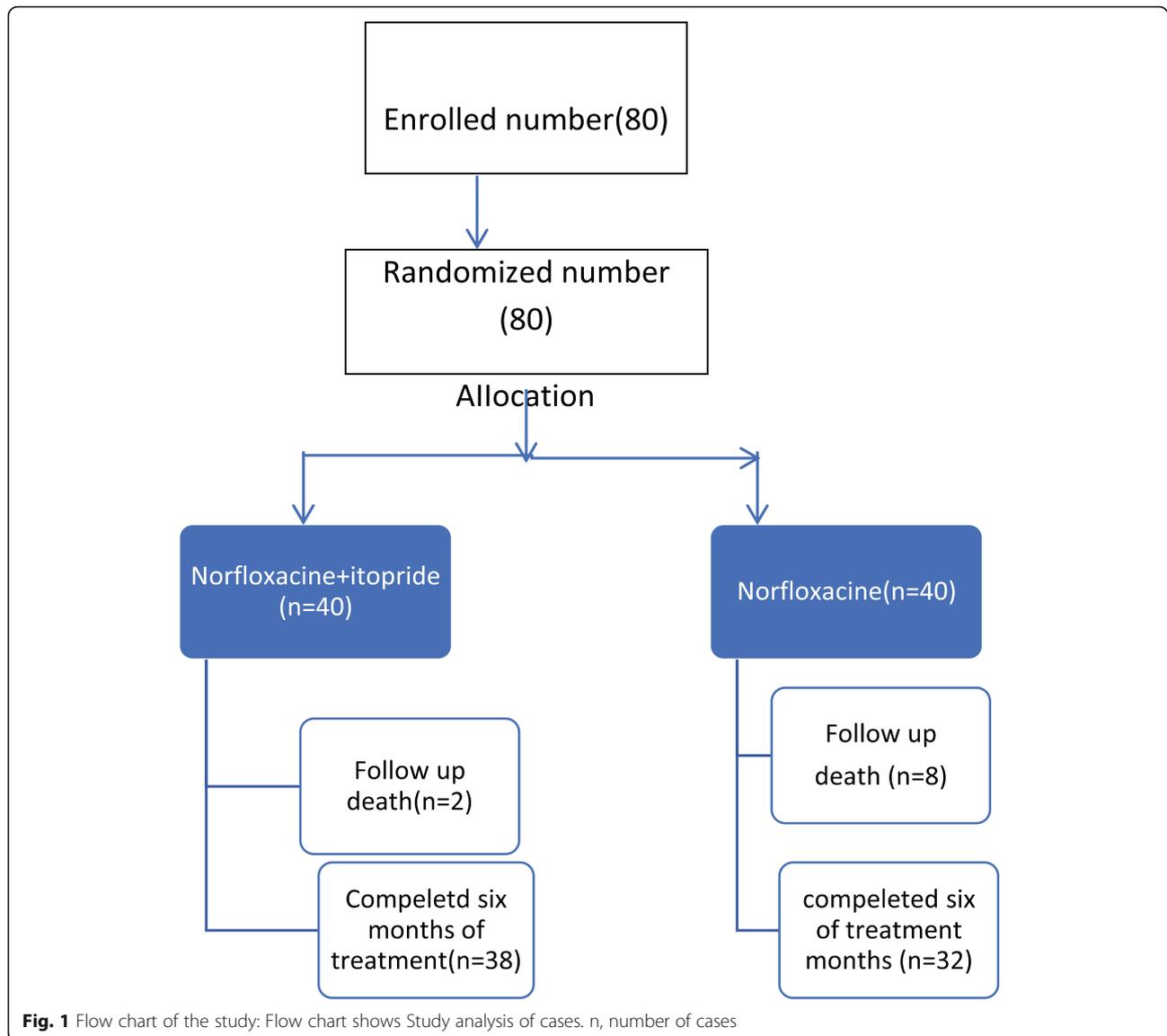
The collected data statistically analyzed by usage of the statistical package for social studies (SPSS) program. These numerical variables included (mean \pm SD) were calculated. The analysis of variance (ANOVA) was used to parallel of mean values between both groups. When ANOVA (F) value was significant, post hoc test (LSD) test could be used to assess the difference between both groups. The comparison of both groups was done by usage (chi-square-test (χ^2) to assess qualitative data; Student *t* test to carry out the significance of the difference in two means of parametric data; and Mann-Whitney *U* test to assess the significance of the difference in both variables of (numerical) non parametric data). The results were represented in tables and graphs. The level of significance was taken at p value of <0.05. P value is either non-significant (NS) if > 0.05, significant (S) if < 0.05, or highly significant (HS) if < 0.001 was calculated.

Results

Our study enrolled 80 patients, 46 men in addition to 34 women and their mean age was 57.50 ± 6.48 years for group I and 59.40 ± 6.16 years for group II (Table 1). As regard to the clinical manifestations which were present in both studied groups, there was no significant difference between both two groups. Regarding the laboratory investigations, there were no significant variances between both studied groups (Table 1).

The ascitic fluid culture of the two studied groups did not show significant difference between both groups. The most frequent organism in both groups was *E. coli* (Table 2).

Table 3 shows the incidence of recurrence of SBP and the cause of death in both groups. There was a significant increase in the occurrence of recurrent SBP in group II with P value (P=0.018*). Also, the number of deaths showed a significant increase in group II P=0.043* and SBP was significantly considered the main factor of death. Table 4 shows the median time for recurrence of SBP in the studied groups which was



significantly longer in group I $P=0.042^*$. Figure 2 shows Kaplan–Meier survival curve which was used to assess the survival among the studied groups. Regarding the side effects of drugs, no side effects were reported by the included patients in both groups.

Discussion

The most common potential life-threatening complications in patients with cirrhosis and ascites is SBP where the mortality rate is alternating between 30 and 50%; hence, the prompt diagnosis and treatment are the most common variable causes in reducing morbidity and mortality of SBP. Bacterial translocation is considered the pathophysiological hallmark in developing spontaneous bacterial peritonitis (SBP). Prokinetics can increase GIT

motility, decrease small bowel transit time, decrease bacterial translocation and the possibility of SBP.

Our study was conducted for evaluating the effectiveness and safety of itopride, as a prokinetic drug, in cirrhotic patients with spontaneous bacterial peritonitis to detect its role in secondary prophylaxis of SBP.

The major strength of this study is that it shed a light about the role of prokinetics in prevention of SBP in cirrhotic ascitic cases through its effect on decreasing the probability of a bacterial overgrowth via increasing the intestinal motility.

In our study, we enrolled 80 cirrhotic ascitic cases with a previous event of SBP who were classified into two groups, each of 40 cases. SBP was common in males in the two studied groups (21 and 25 patients respectively). The mean age was 57.50 ± 6.48 years in group I and

Table 1 Baseline demographic data, clinical manifestations, and the laboratory investigations of both groups

	Group I (itopride + norfloxacin) (number=40) No. (%)	Group II (norfloxacin) (number=40) No. (%)	Test of sig	P value
Age (years) (mean± SD)	57.50 ± 6.48	59.40 ± 6.16	t=1.34	0.183
Gender				
Male	21 (52.5)	25 (62.5)	$\chi^2= 0.81$	0.366
Female	19 (47.5)	15 (37.5)		
Abdominal pain	39 (97.5)	37 (92.5)	FE=1.05	0.615
Fever	31 (77.5)	34 (85.0)	$\chi^2= 0.73$	0.390
Hepatic encephalopathy	8 (20.0)	9 (22.5)	$\chi^2= 0.07$	0.785
Hemoglobin (g/dl)	10.33 ± 1.34	9.83 ± 1.10	t=1.82	0.072
Platelets (cellx 103/mm ³)	122.67 ± 73.03	146.62 ± 77.41	U=1.54	0.122
Total leucocytic count (cellx 103/mm ³)	5.85 ± 3.42	6.51 ± 4.58	U=0.476	0.634
S. creatinine (mg/dl)	1.08 ± 0.58	1.16 ± 0.40	U=1.61	0.106
S urea (mg/dl)	56.47 ± 41.81	52.19 ± 29.86	U=0.09	0.923
AST (u/l)	52.67 ± 36.43	50.70 ± 33.67	U=0.24	0.810
ALT (u/l)	41.82 ± 27.27	36.62 ± 17.36	U=0.28	0.776
S. albumin (g/dl)	2.51 ± 0.50	2.61 ± 0.41	t=0.97	0.335
S. Bilirubin (mg/dl)	2.80 ± 2.68	3.82 ± 3.69	U=0.90	0.368
INR	1.56 ± 0.42	1.65 ± 0.45	t=0.86	0.389
CRP (mg/l)	38.86 ± 37.59	31.00 ± 24.56	U=0.45	0.649

59.40 ± 6.16 years in group II without any a significant difference in both studied groups in age and sex distribution. The two groups were mostly cross-matched.

In this study, the most common symptoms of SBP which presented in both groups were abdominal pain in 39 patients (97.5%) in group I but in 37 cases (92.5%) in group II and fever presented in 31 patients (77.5%) through group I but 34 cases (85%) in group II then vomiting and hepatic encephalopathy (22.5% and 20% respectively) of group I and 40% and 22.5% respectively

of group II without a significant differences in both studied groups as regards the clinical manifestations plus laboratory characteristics of our studied patients. This shows that the patients of both studied groups are cross matched.

In the current work, the degree of ascites in SBP patients was either moderate up or marked. Moderate ascites presented in 32 cases 80% (group I) while (group II) the moderate ascites was detected in 17 cases (42%), while marked ascites was reported in 20% and 57.5% of

Table 2 The patients' ascitic fluid culture analysis

	Group I Number of cases No. (%)	Group II Number of cases No. (%)	Test of sig	P value
Culture result			$\chi^2= 0.07$	0.765
Positive	32 (80.0)	31 (77.5)		
Negative	8 (20.0)	9 (22.5)		
Organisms				
<i>E. coli</i> -G-ve	16 (50.0)	14 (45.2)	FE=0.27	0.965
Klebsiella- G-ve	8 (25.0)	9 (29.03)		
Proteous- G-ve	4 (12.5)	4 (12.9)		
Staph- G+ve	4 (12.5)	3 (9.6)		

χ^2 chi squared test, FE Fisher's exact test

*Significant

Table 3 Incidence of SBP recurrence and causes of death in both groups

Time	Group I number No. (%)	Group II number No. (%)	χ^2	P value
2nd month (n=80)				
SBP free	35 (87.5)	26 (65.0)	5.59	0.018*
SBP	5 (12.5)	14 (35.0)		
4th month (n=72)				
SBP free	34 (89.5)	25 (73.5)	3.08	0.079
SBP	4 (10.5)	9 (26.5)		
6th months (n=70)				
SBP free	34 (87.5)	23 (71.8)	2.49	0.094
SBP	4 (12.5)	9 (28.1)		
Fate (end study)				
Alive	38 (95.0)	32 (80.0)		0.043*
Dead	2 (5.0)	8 (20.0)	4.11	
Causes of death				
HRS	2 (5.0)	5 (12.5)	2.94	0.230
SBP	0 (0.0)	6 (15.0)		
HE	0 (0.0)	3 (7.5)		

*Significant

group I and II respectively with no statistically significant difference in group I and group II. These results corroborate the ideas of [6] who stated that ascitic fluid infection mostly developed when the ascitic fluid volume was at its maximum.

In the current study, patient groups showed low serum albumin level but high serum bilirubin, INR, AST, and ALT levels which mean the most reported cases of that disease (SBP) were Child-Pugh class C in both groups without a statistically significant variance in the studied groups [7].

Diagnostic paracentesis is the main stay in SBP diagnosis and can differ in SBP from secondary peritonitis [8]. It was performed to all cases in groups I and II included in this study. There was no statistically significant variance in the two patient groups according to the ascitic fluid analysis.

Table 4 Median time of recurrence of spontaneous bacterial peritonitis between both studied groups

Group	Mean time (month)			Log-rank test	P value
	Estimate	95% CI			
		Lower	Upper		
Group I (n=39)	5.76	5.41	6.12	4.14	0.042*
Group II (n=36)	5.42	4.90	5.94		
Overall	5.57	5.26	5.87		

*Significant

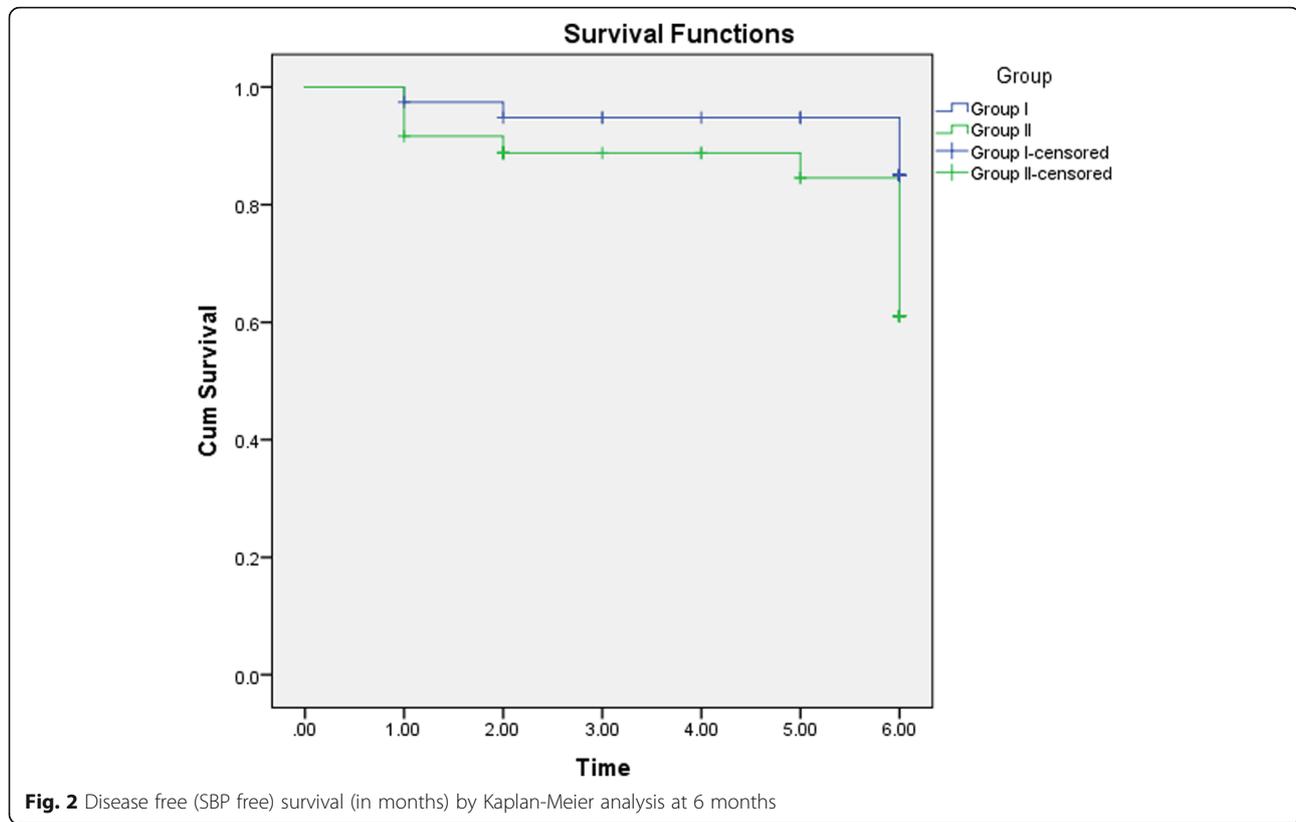
The mean value of serum-ascites albumin gradient (SAAG) in our current study was > 1.1 g/dl in both patient groups which confirmed that the etiology of ascites was portal hypertension in our SBP patients. Agarwal et al. [9] stated that SAAG levels of > 1.1 g/dl confirms that ascites is because of portal hypertension regardless the infection.

As regards to the ascitic fluid culture, the most reported cases of SBP, in both groups, were positive for gram-negative cocci without a statistical significant difference between both groups. These results did not match with Mostafa et al. [10] who found that the majority of their cases of SBP because of gram-positive cocci. In our study, we found that the most common and virulent organisms isolated from the cases were *Escherichia coli* species and Klebsiella but the less common was Staph-Gram-positive cocci, this matched with Novella et al. [11] who observed that of *E. coli* was isolated in 90% of their SBP patients.

In our study, on follow-up of the studied SBP patients, we observed, at the second month, a total of 14 episodes (35%) of recurrent SBP infections in group II (norfloxacin only) versus 5 episodes (12.5%) in group I (norfloxacin plus itopride) with an apparent statistically significant difference. The same variance was also detected in both studied groups in that fourth and sixth month follow-up; however, this difference was not significant. So the usage of both norfloxacin plus itopride (group I) showed a better SBP incidence free through the study follow-up period being 87.5%, 89.5, and 87.5% on the follow-up periods at second, fourth, and sixth month respectively, as compared to that, on usage of norfloxacin only as a SBP secondary prophylactic measure in group II. This accompanied with death of 20% of group II cases compared to death of only 5% of group I cases through the fourth and sixth months follow-up.

According to the present results, regarding the percentage of patients in group I (under treatment with norfloxacin plus itopride) who developed recurrent SBP which represented 12.5%, 10.5%, and 12.5% of cases through the follow-up period at the second, fourth, and sixth months respectively. As a probable explanation for the developing of SBP by the translocation of the bacteria from the intra (intestine) to extra (ascitic fluid) could not be the only route of infection, and the presence of ascitic bacterial DNA can support that condition [12].

In the present study, we reported a 65%, 73.5%, and 71.9% of SBP incidence free through the second, fourth, and sixth months follow-up period respectively in group II who received norfloxacin only. This result matched with Ghafar et al. [13] study that evaluated norfloxacin use in prophylaxis of SBP that established 40% decreasing in the frequency of SBP, among their patients. Also,



Hanouneh et al. [14] found 72% prevention rates of SBP in their study.

On the other hand, Fernandez et al.'s [15] work showed that 93% reducing in the SBP incidence cases, who received norfloxacin. This difference might be due to the type of patients included in our study or the prophylaxis of SBP with norfloxacin only becomes less active as before, because of increasing the incidence of quinolones bacterial resistance in cirrhotic patients flora in the stool due to over use of these drugs [16].

In the current study, the median time for recurrent SBP development was a highly significant prolonged in group I when we compared it by the group II. This was associated with a statistically significant improvement in patient survival rate. The recurrent SBP development rate was significantly decreased in group I (5%) when we compared that by the other group (II) (20%) and that difference in the incidence of SBP recurrence occurred in only in the first 2 months of follow-up due to the number of patient's death increased through the last 4 months that was mainly due to recurrent SBP (15%), HRS (12.5%), and hepatic encephalopathy (7.5%) in group II. While only HRS was reported as the only cause of death in 5% of group I. These results highlight the advantage of using the prokinetics agents (itopride) in combination with norfloxacin in SBP secondary prophylaxis.

The most common causes of mortality all over our study were hepatic encephalopathy, sepsis, and hepatorenal syndrome. And the results showed the beneficial effect of prokinetics (itopride) on group I cases that death in this group was 5% only compared to 20% death rate in group II.

On the same hand, PC Revaiah et al. [17] reported that combined use of prokinetics drugs could considerably reduce the possibility of small intestinal bacterial over growth because of increasing the intestinal motility, which lead to reduce bacterial translocation, the path of bacteria from the intra (intestine) to extra-intestinal such as ascitic fluid and this condition can be useful in SBP prophylaxis and treatment approach.

On other hand, Frazee et al. [18] found that long-term antimicrobial prophylaxis may be useful and has a benefit in cirrhotic patients. However, the magnitude of the benefits was less and the frequency of overall infections and mortality did not change [19].

In the current study, we did not report any side effects from usage of itopride which supported by Huang X (2012), [20] who found that itopride was the least prokinetics agent side effects through the incidence rate of its side effects. Also, itopride had an excitatory influence on the small and large intestine better than cisapride or mosapride [21].

The main limitation of this study is being a single center study with a problem of generalizing the findings. Therefore, larger multicenter studies are crucially

needed to document the role of prokinetic drugs in prevention of SBP.

Conclusions

Norfloracin plus itopride (alkapride) prophylaxis reduced the possibility of development of recurrent SBP in addition to hepatorenal syndrome (HRS) which can precipitated by SBP and that clue why combined therapy improved HRS. This regimen can improve the survival rate in cirrhotic ascitic patients.

Abbreviations

Alb: Albumin; ALT: Alanine transaminase; AST: Aspartate transaminase; BMI: Body mass index; CBC: Complete blood count; DM: Diabetes mellitus; Hb: Hemoglobin; HBV: Hepatitis B virus; HCV: Hepatitis C virus; HTN: Hypertension; No.: Number; PCR: Polymerase chain reaction; PLT: Platelets; SBP: Spontaneous bacterial peritonitis; SD: Standard deviation; SVR: Sustained virological response; WBCs: White blood cells

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Authors' contributions

SA designed the study. SA and MAHS developed the methodology, AYYM, MAHS, and SA wrote the manuscript. AYYM, MAHS, GFA, and SA collected the data. All the authors participated sufficiently in the work and approved the final version of the manuscript. The authors have read and approved the manuscript.

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Availability of data and materials

The authors' institution does not allow public data access.

Declarations

Ethics approval and consent to participate

The research was approved from Tanta University Faculty of medicine Research ethical committee with approval code 30766/7/18. The research also was approved by the ministry of health research ethical committee. An informed written consent was taken from each patient. The study protocol complies with the ethical guidelines of the 1975 Declaration of Helsinki as reflected in prior approval by the institution's Human Research Committee.

Consent for publication

Not applicable.

Competing interests

The authors declare that there is no conflict of interest.

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