

HEPATOLOGY

Spontaneous bacterial peritonitis in cirrhotic patients: Is prophylactic propranolol therapy beneficial?

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Abstract

Background and Aim: It has been suggested that propranolol may have a protective effect on the development of spontaneous bacterial peritonitis by increasing the motility of the bowel and lowering the pressure of the portal vein. The aim of this study is to evaluate the association between the use of propranolol and development of spontaneous bacterial peritonitis in patients with cirrhosis and ascites.

Methods: We retrospectively evaluated 134 patients with cirrhosis and ascites admitted consecutively for a period of 2 years. Diagnosis of spontaneous bacterial peritonitis was based on an ascitic fluid neutrophilic count of $>250/\text{mm}^3$ and/or a positive culture without evidence of secondary peritonitis.

Results: Spontaneous bacterial peritonitis was diagnosed in 39 of 134 (29%) patients and 12 of 39 (31%) patients died in hospital compared to only 4% (four of 95) of those without spontaneous bacterial peritonitis ($P < 0.001$). At admission, patients with spontaneous bacterial peritonitis, as compared to those without, had significantly more encephalopathy (28 vs 11%, $P = 0.02$) or fever (18 vs 4%, $P = 0.01$) and less frequently tense ascites (33 vs 57%, $P = 0.02$). Spontaneous bacterial peritonitis was diagnosed in six of 33 (18%) patients who did and in 33 of 101 (33%) who did not receive propranolol therapy (OR = 0.46, 95% CI: 0.17–1.22, $P = 0.17$).

Conclusion: Our data indicate that spontaneous bacterial peritonitis significantly increases mortality in patients with cirrhosis. Propranolol therapy was not found to be associated with a significantly lower risk for spontaneous bacterial peritonitis, but a Type II statistical error cannot be definitely excluded. The potential protective effect of propranolol on the incidence of spontaneous bacterial peritonitis might deserve evaluation in properly designed prospective studies.

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Key words: ascites, cirrhosis, propranolol, spontaneous bacterial peritonitis.

INTRODUCTION

Spontaneous bacterial peritonitis (SBP) is a severe complication in patients with decompensated liver cirrhosis and ascites, and is associated with high (20–40%) mortality. Moreover, patients with SBP frequently relapse after the first episode, with recurrence in approximately 90% of patients if they are left untreated.^{1,2} The prevalence of SBP in hospitalized patients with cirrhosis ranges between 10 and 30%.¹ The mortality of patients with SBP may have been

reduced lately because of its earlier diagnosis and the availability of more appropriate therapy. However, it is still high because of SBP-related complications, such as renal dysfunction and upper gastrointestinal bleeding.³ Prevention of the first episode of SBP, and its subsequent recurrence, requires the identification of high-risk subgroups of cirrhotic patients, who may benefit from the long- or short-term oral administration of antibiotics. High-risk groups include patients with ascitic fluid protein of less than 1 g/dL, those with previous episodes of SBP and those with active variceal

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bleeding.⁴⁻⁷ Unfortunately, antibiotic prophylaxis for SBP prevention may result in the appearance of resistant bacteria and relapse of peritonitis or bacteremia.⁸

Although the exact pathogenesis of SBP has not yet been identified, translocation of bacteria from the enteric lumen to mesenteric lymph nodes and then to systemic circulation probably plays an important role as an initiating event of SBP,⁹ because it results in colonization of the ascitic fluid and a subsequent inflammatory reaction of the peritoneum.¹⁰ Recently, experimental studies in animal models of portal hypertension have suggested that propranolol may reduce the incidence of SBP, as a result of higher intestinal transit and reduction of bacterial translocation from the bowel to systemic circulation.¹¹ The effect of propranolol on the incidence of SBP has not been adequately studied in humans, although beta-blockers are commonly prescribed in cirrhotic patients with esophageal varices for primary or secondary prevention of variceal bleeding.

This study aims to evaluate the effect of propranolol treatment on the incidence of SBP in cirrhotic patients with ascites.

METHODS

We retrospectively evaluated 134 patients with decompensated cirrhosis and ascites, who were consecutively admitted to our department (the Second Department of Internal Medicine at Hippokraton Hospital of Athens, University of Athens, Greece) between June 1999 and June 2001. At admission, all patients had a diagnostic paracentesis and ascitic fluid culture taken. Patients with a previous history of SBP or antibiotic administration during the week before inclusion in the study were excluded. Patients with more than one admission during the study period were evaluated in the analysis only at their first admission. On the day of admission, a detailed medical history, in particular the patient's use of propranolol, a complete physical examination and a battery of laboratory tests, including complete blood count, prothrombin time, and biochemical tests of liver and kidney function, were performed. The diagnosis of SBP was based on the presence of an ascitic fluid polymorphonuclear leukocyte count equal or greater than 250 cells/mm³ and/or positive ascitic fluid cultures, in the absence of clinical and laboratory evidence suggesting secondary peritonitis.

The following 18 variables, possibly related to SBP, were considered for the uni- and multivariate analysis: sex, age, cause of cirrhosis, Child class and Child-Pugh score, cause of admission (tense ascites, encephalopathy, fever, upper gastrointestinal system bleeding), history of a previous complication of cirrhosis, administration of propranolol as well as on admission values of white blood and platelet count, serum creatinine, alanine aminotransferase, aspartate aminotransferase, alkaline phosphatase, gamma-glutamyl-transpeptidase, total bilirubin, prothrombin time, serum albumin and laboratory characteristics of ascitic fluid (polymorphonuclear leukocyte count, total protein, albumin, glucose and cholesterol).

Statistical analysis

All data were analyzed by using the statistical package SPSS (version 10.0; SPSS Inc., Chicago, IL, USA). The chi-squared test was used for comparison of qualitative variables and the Student's *t*-test and Wilcoxon signed-rank test for comparisons of quantitative variables, when appropriate. Quantitative variables with a normal distribution were expressed as mean values \pm one standard deviation (SD), and those with a non-normal distribution as median value (range). Significance level was two-sided and set to less than 0.05. Variables close to or under the statistical significance level in the univariate analysis ($P \leq 0.10$) were included in the multivariate analysis using logistic regression models.

RESULTS

Clinical characteristics of the 134 patients

There were 94 men and 40 women with a mean age of 64 ± 12 years. The cause of cirrhosis was chronic infection with hepatitis B virus (HBV) in 49 (37%), chronic infection with hepatitis C virus (HCV) in 27 (20%), alcohol abuse in 28 (21%), primary biliary cirrhosis in one (0.5%), primary sclerosing cholangitis in one (0.7%) and unknown (cryptogenic cirrhosis) in 28 (21%) patients. Twelve (9%) patients had Child class A, 79 (59%) class A and 43 (32%) class C cirrhosis. SBP was diagnosed in 39 (29%) patients. The baseline characteristics of the patients with and without SBP are shown in Table 1.

Predictive factors for the presence of SBP

The presence of SBP was found to be significantly associated with the presence of encephalopathy, fever and tension ascites on admission (Table 1). In particular, patients with SBP compared with those without SBP, were admitted more often for encephalopathy (11 of 39 (28%) vs 10 of 95 (11%), $P = 0.02$) or fever (seven of 39 (18%) vs four of 95 (4%), $P = 0.01$) and less frequently for tense ascites (13 of 39 (33%) vs 54 of 95 (57%), $P = 0.02$).

Effect of treatment with propranolol in the incidence of SBP

Thirty-three (24.6%) of the 134 patients had been receiving treatment with propranolol. The subgroup of propranolol-treated patients was similar to the subgroup of the patients not taking propranolol in relation to their clinical characteristics and risk factors for SBP (Table 2). The incidence of SBP tended to be lower in patients on propranolol, but the difference was not significant. In particular, SBP was diagnosed in six of 33 (18%) patients on propranolol and in 33 of 101 (33%) patients who did not receive previous propranolol

Table 1 Baseline characteristics of patients with or without spontaneous bacterial peritonitis (SBP)

Patient characteristics	SBP (<i>n</i> = 39)	No-SBP (<i>n</i> = 95)	<i>P</i>
Age (years)	64 ± 12	68 ± 12	0.69
Sex (male/female)	26/13	68/27	0.77
Cause of cirrhosis, <i>n</i> (%)			0.37
HBV	11 (28)	38 (40)	
HCV	9 (23)	18 (19)	
Alcohol	8 (21)	20 (21)	
PBC/PSC	2 (5)	0 (0)	
Unknown	9 (23)	19 (20)	
Cause of admission, <i>n</i> (%)			0.003
Tension ascites	13 (33)	54 (57)	
Encephalopathy	11 (28)	10 (11)	
Bleeding	3 (6)	15 (16)	
Fever	7 (20)	4 (3)	
Other	5 (13)	12 (13)	
Complications of cirrhosis, <i>n</i> (%)			0.41
None	15 (38)	48 (50)	
Gastrointestinal bleeding	11 (28)	18 (19)	
Encephalopathy	4 (11)	6 (7)	
HCC	9 (23)	23 (24)	
Child–Pugh class, <i>n</i> (%)			0.82
A	3 (8)	9 (9)	
B	22 (56)	57 (60)	
C	14 (36)	29 (31)	
White blood count (× 10 ⁹ /L)	9.1 ± 4.6	7.9 ± 3.8	0.11
Platelet count (× 10 ⁹ /L)	145 ± 83	140 ± 77	0.85
Prothrombin time (s)	17 ± 4.9	16.8 ± 6.6	0.77
Creatinine (mg/dL)	1.4 (0.7–5.6)	1.3 (0.7–5.9)	0.84
Bilirubin (mg/dL)	4.2 (1.1–33.9)	3.3 (0.7–43.7)	0.06
AST (IU/L)	88 (17–670)	88 (19–840)	0.76
ALT (IU/L)	73 (11–450)	44 (13–980)	0.86
ALP (U/L)	129 (37–1270)	141 (19–788)	0.64
GGT (U/L)	80 (21–844)	95 (14–1015)	0.97
Albumin (g/dL)	3.1 ± 0.55	3.0 ± 0.5	0.85
Ascitic fluid			
Protein (g/dL)	1.6 (0.5–6.4)	1.6 (0.4–4)	0.28
Albumin (g/dL)	0.9 (0.2–3.3)	0.6 (0.1–2.3)	0.22
Glucose (mg/dL)	121 (32–279)	133 (78–467)	0.04
Cholesterol (mg/dL)	21 (5–107)	22 (5–63)	0.62
Patients under propranolol, <i>n</i> (%)	6 (15)	27 (28)	0.17
Propranolol dose (mg/day)	45 ± 19.1	36.6 ± 15.2	0.34

ALT, alanine aminotransferase; ALP, alkaline phosphatase; AST, aspartate aminotransferase; GGT, gamma-glutamyl-transpeptidase; HBV, hepatitis B virus; HCC, hepatocellular carcinoma; HCV, hepatitis C virus; PBC, primary biliary cirrhosis; PSC, primary sclerosing cholangitis.

therapy (OR = 0.46, 95% CI: 0.17–1.22, *P* = 0.17; Table 2).

Factors associated with mortality

Sixteen (12%) of the 134 patients died in hospital; in particular, 31% (12 of 39) of patients with SBP and only 4% (four of 95) of the patients without SBP (*P* < 0.001). In univariate analysis, the Child–Pugh score, presence of encephalopathy on admission, presence of SBP, white blood count, bilirubin levels and

prothrombin time were found to be significantly associated with mortality (Table 3). Multivariate analysis showed that mortality was independently associated only with prothrombin time (*P* = 0.036) and presence of SBP (*P* = 0.0003).

DISCUSSION

The presence of SBP was found to have a significant negative predictive value on patient survival. In partic-

Table 2 Baseline characteristics of patients with cirrhosis with ascites in relation to their treatment with propranolol

Patient characteristics	No propranolol (<i>n</i> = 101)	On propranolol (<i>n</i> = 33)	<i>P</i>
Age (years)	64 ± 12	63 ± 9.4	0.68
Sex (male/female)	72/29	22/11	0.61
Cause of cirrhosis, <i>n</i> (%)			0.47
HBV	35 (34)	14 (42)	
HCV	21 (21)	6 (18)	
Alcohol	25 (25)	3 (9)	
PBC/PSC	1 (1)	1 (3)	
Unknown	19 (19)	9 (28)	
Cause of admission, <i>n</i> (%)			0.63
Tension ascites	51 (50)	16 (49)	
Encephalopathy	16 (16)	5 (15)	
Bleeding	13 (13)	5 (15)	
Fever	10 (10)	1 (3)	
Other	11 (11)	6 (18)	
Complications of cirrhosis, <i>n</i> (%)			0.63
None	50 (49)	13 (39)	
Gastrointestinal bleeding	19 (19)	10 (30)	
Encephalopathy	8 (8)	2 (6)	
HCC	24 (24)	8 (25)	
Child–Pugh class, <i>n</i> (%)			0.97
A	9 (9)	3 (9)	
B	59 (58)	20 (61)	
C	33 (33)	10 (30)	
White blood count (× 10 ⁹ /L)	8.4 ± 4.1	7.7 ± 3.6	0.37
Platelets (× 10 ⁹ /L)	130 ± 84	100 ± 75	0.25
Prothrombin time (s)	16.9 ± 6.8	16.7 ± 3.5	0.87
Creatinine (mg/dL)	1.3 (0.7–5.9)	1.5 (0.8–3.1)	0.19
Bilirubin (mg/dL)	3.5 (0.3–43.7)	3.4 (0.7–28.9)	0.66
AST (IU/L)	88 (17–839)	55 (25–545)	0.16
ALT (IU/L)	47 (11–980)	45 (16–309)	0.89
ALP (U/L)	134 (37–1270)	179 (19–511)	0.18
GGT (U/L)	80 (14–1015)	128 (25–417)	0.28
Albumin (g/dL)	3 ± 0.47	3.1 ± 0.58	0.29
Ascitic fluid			
Protein (g/dL)	1.5 (0.4–6.4)	1.4 (0.6–4)	0.75
Albumin (g/dL)	0.7 (0.1–3.3)	0.6 (0.2–2.1)	0.92
Glucose (mg/dL)	130 (35–353)	134 (32–467)	0.17
Cholesterol (mg/dL)	22 (5–107)	20 (10–42)	0.85
SBP, <i>n</i> (%)	33 (32)	6 (18)	0.17

ALT, alanine aminotransferase; ALP, alkaline phosphatase; AST, aspartate aminotransferase; GGT, gamma-glutamyl-transpeptidase; HBV, hepatitis B virus; HCC, hepatocellular carcinoma; HCV, hepatitis C virus; PBC, primary biliary cirrhosis; PSC, primary sclerosing cholangitis; SBP, spontaneous bacterial peritonitis.

ular, 31% of patients with SBP and 4% of those without SBP died during hospitalization. Such a high mortality in patients with SBP ranging between 20 and 40% has also been reported by others.² Thus, SBP remains a serious complication in cirrhotic patients despite much progress in the management of such patients.

Although the precise pathogenesis of SBP has not yet been elucidated, SBP is considered to be associated with the translocation of enteric bacterial flora (mainly Gram-negative enterobacteria) to mesenteric lymph nodes, then to systemic circulation and finally to peritoneal cavity.^{9,10} The increased transfer of bacteria from

enteric lumen to bloodstream is facilitated by two factors: (i) the increased permeability of intestinal epithelia; and (ii) the low motility of the bowel. According to experimental data, tight junctions of enteric mucosa have a functional defect as a result of portal hypertension. The higher the portal pressure, the easier the transfer of bacteria from enteric lumen to mesenteric lymph nodes.^{12,13} Low intestinal motility is mediated by topical factors such as nitric oxide (a potent vasodilator)¹⁴ and by systemic factors such as hyperactivity of autonomic sympathetic nervous system.¹⁵ Intense activation of both factors causes enteric hypomotility,

Table 3 Baseline characteristics of patients with cirrhosis with ascites in relation to their in hospital survival

Patient characteristics	Died (<i>n</i> = 16)	Survived (<i>n</i> = 118)	<i>P</i>
Age (years)	62.8 ± 8.8	64 ± 12	0.74
Sex (male/female)	12/4	82/36	0.87
Cause of cirrhosis, <i>n</i> (%)			0.24
HBV	6 (37)	43 (36)	
HCV	6 (37)	21 (18)	
Alcohol	4 (26)	24 (21)	
PBC/PSC	0 (0)	2 (1)	
Unknown	0 (0)	28 (24)	
Cause of admission, <i>n</i> (%)			0.002
Tension ascites	4 (25)	63 (53)	
Encephalopathy	8 (50)	13 (11)	
Bleeding	1 (6)	17 (15)	
Fever	1 (6)	10 (8)	
Other	2 (13)	15 (13)	
Complications of cirrhosis, <i>n</i> (%)			0.93
None	6 (37)	57 (48)	
Gastrointestinal bleeding	4 (25)	25 (21)	
Encephalopathy	2 (13)	8 (7)	
HCC	4 (25)	28 (24)	
Child–Pugh class, <i>n</i> (%)			0.016
A	0 (0)	12 (10)	
B	6 (38)	73 (62)	
C	10 (62)	33 (28)	
White blood count ($\times 10^9/L$)	11.1 ± 4.3	7.8 ± 3.8	0.003
Platelet count ($\times 10^9/L$)	143 ± 86	141 ± 77	0.98
Prothrombin time (s)	21.9 ± 14	16.2 ± 3.7	<0.001
Creatinine (mg/dL)	1.55 (0.7–5)	1.3 (0.7–5.9)	0.13
Bilirubin (mg/dL)	8 (1.9–33.9)	3.3 (0.3–43.7)	0.004
AST (IU/L)	130 (17–670)	87.5 (19–839)	0.31
ALT (IU/L)	49 (16–450)	46 (11–980)	0.93
ALP (U/L)	97 (49–845)	140 (19–1270)	0.34
GGT (U/L)	128 (21–1015)	76 (14–844)	0.11
Albumin (g/dL)	2.95 ± 0.57	3.046 ± 0.49	0.51
Ascitic fluid			
Protein (g/dL)	1.55 (0.7–6.4)	1.5 (0.4–5)	0.62
Albumin (g/dL)	0.9 (0.2–3.3)	0.7 (0.1–2.7)	0.91
Glucose (mg/dL)	133 (32–320)	130 (74–467)	0.56
Cholesterol (mg/dL)	20 (6–107)	22 (5–74)	0.93
Propranolol therapy, <i>n</i> (%)	14 (88)	87 (74)	0.37
SBP, <i>n</i> (%)	12 (75)	27 (23)	<0.001*

*OR: 10.1, 95% CI: 3–34.0. ALT, alanine aminotransferase; ALP, alkaline phosphatase; AST, aspartate aminotransferase; GGT, gamma-glutamyl-transpeptidase; HBV, hepatitis B virus; HCC, hepatocellular carcinoma; HCV, hepatitis C virus; PBC, primary biliary cirrhosis; PSC, primary sclerosing cholangitis; SBP, spontaneous bacterial peritonitis.

which becomes more pronounced as portal hypertension and liver failure advances, resulting in overgrowth of Gram-negative bacteria in the bowel.^{16,17}

Propranolol, and other non-selective beta-blockers of the sympathetic nervous system, have been found to reduce portal pressure and are widely used in cirrhotic patients for primary and secondary prevention of variceal bleeding.¹⁸ Propranolol could be expected to have a beneficial effect on the occurrence of SBP by: (i) increasing the motility of the bowel by its sympatholytic action; and (ii) lowering the portal pressure and

indirectly decreasing microbial translocation to systemic circulation.

The effect of propranolol on the development of SBP has been recently studied in an experimental animal model of portal hypertension.¹¹ Propranolol was found to increase bowel motility and reduce the overgrowth of enteric bacteria flora, the translocation of microbia in systemic circulation and the development of SBP. In two other studies, the use of cisapride, a prokinetic agent, also resulted in the prevention of SBP development probably because of the improvement of small

bowel motility in an experimental cirrhotic animal model.^{19,20}

In this retrospective study, we evaluated the possible protective effect of propranolol therapy on the development of SBP in cirrhotic patients with ascites. In our cohort, long-term administration of propranolol, which had been given as primary or secondary prophylaxis of variceal bleeding, was associated with a lower incidence of SBP (18 vs 33%), but the difference was not significant. The number of patients in the present study, however, was relatively small (134 patients) with only 25% of them receiving propranolol, and therefore the lack of a significant statistical difference may be related to a statistical Type II error, rather than to a real absence of beneficial effect. We estimated that at least 137 patients per group would be required for a trial to have reasonable power (Type I error = 0.05, Type II error = 0.20) to give significant results for a difference between the two groups similar to that observed in the present study. In another recently published retrospective study including only 73 patients, the incidence of SBP was also lower in patients taking propranolol (47%) than in controls (54%), but the difference again was not significant.²¹ However, in a recent prospective study, Chelarescu *et al.* evaluated again 73 cirrhotic patients, who underwent laparoscopic surgery and found that patients with cirrhosis who received ciprofloxacin plus propranolol (starting just before surgery), compared to those who received only ciprofloxacin, had a significantly lower incidence of postsurgical infection (14.7 vs 42.4%, $P < 0.05$).²²

The dose of beta-blocker may play an important role on the development of SBP. In the study by Perez-Paramo *et al.*, propranolol was given at a dose of 10 mg/kg per day, which is much higher than the usual dose of propranolol given in clinical practice to prevent variceal bleeding in patients with cirrhosis.¹¹ Although the propranolol dose was not found to affect the incidence of SBP development in the present study (Table 1), it should be noted that propranolol was always given for the prevention of variceal bleeding, and that prevention of SBP might necessitate higher doses. A beneficial effect, therefore, on SBP of higher propranolol doses cannot be definitely excluded, if such doses can be tolerated by the patients.

In conclusion, although propranolol treatment did not seem to be a significant factor for the prevention of SBP in patients with cirrhosis and ascites, it is possible that a significant effect might be hidden by a statistical Type II error. Thus, the possible beneficial effect of propranolol on the incidence of SBP deserves to be evaluated in a properly designed prospective, larger, controlled trial.

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