

# Nadolol Plus Spironolactone in the Prophylaxis of First Variceal Bleed in Nonascitic Cirrhotic Patients: A Preliminary Study

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Treatment with  $\beta$ -blockers fails to decrease portal pressure in nearly 40% of cirrhotic patients. Recent studies have suggested that treatment with spironolactone reduces pressure and flow in the portal and variceal systems. This trial was designed to assess if nadolol plus spironolactone is more effective than nadolol alone to prevent the first variceal bleeding. One hundred patients with medium and large varices who had never bled and were without ascites were included in a prospective, randomized, multicenter, double-blind, placebo-controlled trial. The patients were randomized into 2 groups: 51 received nadolol plus placebo (N + P) and 49 received nadolol plus spironolactone 100 mg/d (N + S). Hepatic venous pressure gradient (HVPG) and activity of the renin-aldosterone system (plasma renin activity/plasma aldosterone levels) were measured in 24 patients. There were no significant differences in the appearance of variceal bleeding and ascites between groups at a mean follow-up of  $22 \pm 16$  months. However, analyzing both complications together, the incidence was significantly higher in the N + P group than in the N + S group (39% vs. 20%;  $P < .04$ ). Clinical ascites was also higher in patients in the N + P group than in the N + S group (21% vs. 6%;  $P < .04$ ). Significant increases in plasma renin activity and plasma aldosterone levels were only observed in patients in the N + S group ( $P < .01$ ). The cumulative probabilities of remaining free of bleeding and ascites were similar in both groups after 70 months of follow-up. In conclusion, these results suggest that nadolol plus spironolactone does not increase the efficacy of nadolol alone in the prophylaxis of the first variceal bleeding. However, when bleeding and ascites were considered together, the combined therapy effectively reduced the incidence of both portal-hypertensive complications. (HEPATOLOGY 2003;37:359-365.)

At present, nonselective  $\beta$ -adrenergic blockers ( $\beta$ -blockers) are the drugs of choice to prevent the first variceal bleeding in cirrhotic patients with large esophageal varices.<sup>1</sup> Previous studies have shown that reduction of the hepatic venous pressure gradient

(HVPG) to less than 12 mm Hg or a decrease in HVPG greater than 20% from basal values protects against variceal hemorrhage. However, such a decrease in portal pressure could be achieved in only 20% of patients receiving  $\beta$ -blockers.<sup>2</sup> Moreover, 40% of treated patients do not have reduced portal pressure despite adequate  $\beta$ -blockade.<sup>3</sup> Therefore, the addition of drugs to  $\beta$ -blockers has been investigated to achieve effective reductions in portal pressure in a greater proportion of patients.<sup>4</sup>

Recent data have shown that spironolactone significantly lowers portal and variceal pressures by reducing plasma volume and splanchnic blood flow.<sup>5-9</sup> Plasma volume depletion improves the hyperdynamic circulatory state associated with the development and maintenance of portal hypertension.<sup>10,11</sup> However, a correlation could not be shown between the decrease in circulating plasma volume and the decrease in HVPG.<sup>5,6,8</sup> It has been suggested that spironolactone may also have a direct vasoactive effect on the splanchnic circulation that is not mediated by its antialdosteronic mechanism.<sup>12</sup>

Abbreviations: HVPG, hepatic venous pressure gradient; N + P, nadolol plus placebo; N + S, nadolol plus spironolactone.

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The decrease in portal pressure achieved by administration of spironolactone could be found even in patients without ascites<sup>5-7</sup> and with or without a restricted sodium diet.<sup>6-8</sup> The acute addition of intravenous propranolol to long-term spironolactone therapy (100 mg/d) further decreased HVPG.<sup>7</sup> Furthermore, the combination of spironolactone and propranolol significantly reduced variceal pressure in the subset of patients unresponsive to propranolol alone.<sup>9</sup>

However, whether these hemodynamic effects have any impact on the management of cirrhotic patients with portal hypertension has never been assessed in long-term clinical trials. Therefore, the aim of this study was to compare the nonselective  $\beta$ -blocker nadolol with spironolactone plus nadolol in the primary prophylaxis of variceal bleeding. We also investigated whether the combined treatment would have a beneficial effect to prevent the first appearance or recurrence of ascites.

## Patients and Methods

**Patients.** From October 1993 to December 1999, 100 patients seen in 5 centers in Argentina were enrolled: 45 in Hospital B. Udaondo, 36 in Hospital Posadas, 8 in Hospital Ramos Mejía, 6 in Hospital Israelita, and 5 in Hospital Municipal. The inclusion criteria were as follows: (1) a diagnosis of cirrhosis based on clinical and biochemical data, ultrasonography, and liver biopsy when the procedure was not contraindicated; (2) medium and large esophageal varices irrespective of the presence of red color signs<sup>13</sup>; (3) no history of variceal bleeding; (4) ultrasonographic absence of ascites; and (5) no diuretic treatment for at least 1 month before inclusion in the trial. The exclusion criteria were as follows: (1) contraindications to administration of  $\beta$ -blockers (heart rate  $<55$  beats/min, systolic blood pressure  $<85$  mm Hg, chronic obstructive lung disease, psychosis, insulin-dependent diabetes with history of hypoglycemia, heart failure, and second- or third-degree atrioventricular blocks); (2) hepatocellular carcinoma or other malignancies; (3) serum urea and/or creatinine levels greater than 50 and 1.5 mg/dL, respectively; (4) bacterial infections; and (5) chronic hepatic encephalopathy. According to these criteria, 100 of 170 consecutive patients were eligible for this study. Reasons for exclusion were as follows: small varices ( $n = 10$ ), previous variceal bleeding ( $n = 15$ ), ascites ( $n = 11$ ), small varices and ascites ( $n = 10$ ), contraindications to  $\beta$ -blockers ( $n = 12$ ), chronic encephalopathy ( $n = 3$ ), tumors ( $n = 6$ ), and refusal to participate in the study ( $n = 3$ ).

The study was designed as a randomized, multicenter, prospective, double-blinded trial. The protocol, which conformed with the Helsinki Declaration, was approved

by the hospital ethical committee of each center, and patients gave their written informed consent to participate in the investigation. Randomization was performed by tables of random numbers at the coordinating center and stratified according to participating hospitals.

**Protocol.** After randomization, patients were treated with nadolol at increasing doses to reduce resting heart rate by 25% or to 55 beats/min. Once the suitable dose was achieved, 51 patients treated with nadolol alone (N + P) received a placebo tablet and 49 patients treated with nadolol plus spironolactone (N + S) received spironolactone at a fixed dosage of 100 mg/d for the whole study. Spironolactone and placebo, in identical tablets, were given by an assistant not directly involved with the protocol to ensure study blindness. Treatment was administered once daily at breakfast. All patients were following an unrestricted-sodium diet. Compliance with treatment was assessed by checking persistence of heart rate reduction and counting the remaining tablets at each visit. Patients who consumed less than 85% of prescribed pills were classified as noncompliant.

Patients were followed up monthly with a physical examination as well as measurement of heart rate and arterial blood pressure and every 2 and 6 months with biochemical evaluation and abdominal ultrasonography, respectively, for the first 2 years. Thereafter, the clinical evaluation was performed every 3 months and the biochemical parameters and ultrasonography every 6 months until end point or December 1999.

A hemodynamic study was performed in 12 patients in each group before and after 2 to 3 months of treatment. After an overnight fast and under local anesthesia, a 7F venous catheter introducer was placed in the right femoral vein by the Seldinger technique. Under fluoroscopy, a 7F balloon-tipped catheter (Medi Tech; Cooper Scientific Corp., Watertown, MA) was advanced into the main right hepatic vein. Wedge (occluded) and free hepatic venous pressures were measured by inflating and deflating the balloon. Afterward, a 7F Swan-Ganz catheter (Edwards Laboratory, Los Angeles, CA) was placed into the pulmonary artery to measure cardiopulmonary pressures and cardiac output (thermodilution). Arterial pressure was recorded by a sphygmomanometer attached to the right arm of the patient, who was in the supine position, and heart rate was derived from the continuous electrocardiographic monitoring. All parameters were measured at least in triplicate, and tracings were obtained on a multichannel recorder (Electronics Inc., Pleasantville, NY). Portal pressure was estimated from the HVPG, the difference between wedge hepatic venous pressure and free hepatic venous pressure. Systemic vascular resistance ( $\text{dyne} \cdot \text{s} \cdot \text{cm}^{-5}$ ) was calculated as  $(\text{MAP} - \text{right atrial pressure})/$

CO  $\times$  80 in which MAP indicates mean arterial pressure (mm Hg) and CO indicates cardiac output (L/min).<sup>14</sup>

After an overnight fast and 2 hours of bed rest, blood samples from 12 patients in each group were taken to measure plasma renin activity and plasma aldosterone levels. Samples were collected in tubes containing ethylenediaminetetraacetic acid that were placed on ice and centrifuged at 4°C, and the plasma was frozen at -30°C until assayed. Plasma renin activity (normal value, 0.2-2.8 ng/mL/h) and plasma aldosterone levels (normal value, 35-350 pg/mL) were measured by radioimmunoassay before and after 18 months of treatment.

The primary end point of the trial was variceal bleeding. Secondary end points were appearance of ascites, adverse effects requiring withdrawal from treatment, and survival. We diagnosed variceal bleeding when (1) a patient with hematemesis and/or melena showed varices actively bleeding or with a white nipple or a clot on a varix or (2) varices without another potential source of bleeding were identified at emergency endoscopy performed within the first 24 hours of the hemorrhage.<sup>1</sup> These patients were treated with sclerotherapy and were withdrawn from the trial. Patients who developed either minimal ascites, only detectable by ultrasonography, or clinical ascites were also withdrawn from the trial. Criteria used for discontinuation of therapy were as follows: symptomatic arterial hypotension or systolic blood pressure less than 85 mm Hg; heart failure; encephalopathy without improvement despite a low-protein diet and lactulose therapy; bronchospasm; arrhythmia; severe painful gynecomastia; serum urea and/or creatinine levels greater than 50 and 1.5 mg/dL, respectively; hyponatremia (a decrease in serum sodium >5 mEq/L to a level <130 mEq/L); or hyperkalemia (an increase >1.5 mEq/L to a level >5 mEq/L).

**Statistical Analysis.** Taking into account that no long-term clinical data are available regarding the effects of spironolactone on portal pressure and that patients with large esophageal varices treated with  $\beta$ -blockers would have an expected risk of bleeding of 31% during a follow-up of at least 2 years, we considered it clinically relevant to decrease this risk to 12%. In that regard, we estimated a sample size of 145 patients given an  $\alpha$  error of 0.05 and a  $\beta$  error of 0.2 in a 2-tailed test. An interim analysis was planned when most patients completed at least 2 years of follow-up.

Comparisons between groups were performed using nested ANOVA test for quantitative variables and  $\chi^2$  test for qualitative variables. The cumulative probabilities of variceal bleeding, ascites, and survival were calculated using the Kaplan-Meier method and compared by log-rank test. Predictors of bleeding were identified by Cox's re-

**Table 1. General Characteristics of Included Patients**

	N + P (n = 51)	N + S (n = 49)
Age (yr)	56 $\pm$ 10	59 $\pm$ 11
Sex (M/F)	29/22	26/23
Alcohol consumption (%)	53	39
Child-Pugh score	5.8 $\pm$ 1.0	6.0 $\pm$ 1.0
Child-Pugh class (A/B/C)	43/7/1	39/10/0
Esophageal varices (GII/III)	43/8	35/14
Previous ascites (n)	11	8
Mean dosage of nadolol (mg/d)	80 $\pm$ 60	76 $\pm$ 62*
Mean follow-up (mo)	21 $\pm$ 15	23 $\pm$ 18†

NOTE. No significant difference was observed between groups.

\*Range of 10-240 mg/d in both groups.

†Range of 3-60 months in the N + P group and 1-70 months in the N + S group.

gression model. The following variables were assessed: type of treatment, age, sex, cause of cirrhosis, Child-Pugh score, previous ascites, and dosage of nadolol. *P* values less than .05 were considered significant. Results are given as mean  $\pm$  SD. Data were analyzed according to the intention-to-treat strategy.

## Results

There were no significant differences in demographic, etiologic, clinical, and endoscopic characteristics; previous episodes of ascites; mean dosage of nadolol (78  $\pm$  61 mg/d); and mean follow-up (22  $\pm$  16 months) between both groups of patients (Table 1).

During the study, 6 patients (3 in each group) were lost to follow-up: 4 patients in the first 6 months and 2 patients at 12 and 18 months, respectively.

Five patients in the N + P group and 4 patients in the N + S group had to be withdrawn from treatment because of adverse effects of  $\beta$ -blockers: 3 because of bradyarrhythmia, 3 because of bronchospasm, one because of symptomatic hypotension, one because of encephalopathy, and one because of postural dizziness and severe asthenia. Five patients were withdrawn during the first 6 months of treatment, and the remaining 4 were withdrawn after 24 months of follow-up. Two patients with side effects of spironolactone (hyperkalemia [potassium, 6 mmol/L] and serum creatinine level of 1.7 mg/dL) were withdrawn at 6 and 15 months of treatment. These complications disappeared after discontinuation of the relevant drug. Minor adverse effects that did not preclude continuation with treatment included mild asthenia in 9 patients, gynecomastia in 4 patients (2 in each group), dizziness in 3 patients, arterial hypotension in 7 patients, and encephalopathy stage I in 3 patients, with similar distribution in both groups (Table 2).

Inadequate compliance was observed in 4 patients in the N + P group and 5 patients in the N + S group.

**Table 2. Side Effects During the Study**

	N + P (n = 51) n (%)	N + S (n = 49) n (%)
Asthenia	5 (10)	5 (10)
Dizziness	2 (4)	2 (4)
Hypotension	2 (4)	6 (11)
Encephalopathy	2 (4)	2 (4)
Bronchospasms	1 (2)	2 (4)
Gynecomastia	2 (4)	2 (4)
Renal failure	—	2 (4)
Bradycardia	3 (6)	—
Patients requiring withdrawal	5 (10)	6 (11)

NOTE. No significant difference was observed between groups.

Hepatic and renal function test results and electrolyte levels were similar before and after treatment in both groups. Treatment with nadolol alone did not produce any changes in plasma renin activity and plasma aldosterone levels. In contrast, the addition of spironolactone to nadolol was associated with significant increases in both parameters (Table 3).

**Splanchnic Hemodynamics.** In patients in the N + P group, HVPG decreased significantly from  $16.3 \pm 3.7$  mm Hg at baseline to  $14.3 \pm 3.5$  mm Hg after treatment (mean decrease,  $-11.5 \pm 14.4\%$ ;  $P < .05$ ). Patients in the N + S group showed a significant reduction in HVPG from  $17.9 \pm 2.7$  to  $15 \pm 3.3$  mm Hg (mean decrease,  $-16 \pm 12.4\%$ ;  $P < .01$ ). No significant differences were observed when the decrease in HVPG was compared between groups (Table 4).

**Systemic Hemodynamics.** Both groups of patients showed effective  $\beta$ -blockade, evidenced by a significant reduction in cardiac output and heart rate in addition to an increase in systemic vascular resistance. A small but significant decrease in mean arterial pressure was observed

in the N + S group (Table 3). There were no changes in cardiopulmonary pressures in both groups of patients.

**Clinical Outcome.** During follow-up, 7 patients in the N + P group (13.7%) and 3 patients in the N + S group (6%) had variceal bleeding. Eight patients bled from esophageal varices (6 in the N + P group and 2 in the N + S group), either on medium or large varices. These patients were treated with sclerotherapy. The remaining 2 patients (one in each group) bled from gastric varices, and one of them received a portocaval shunt. The cumulative probabilities of patients to be free of bleeding after 70 months of follow-up were 73% in the N + P group and 79% in the N + S group ( $P = NS$ ) (Fig. 1).

Ascites developed in 13 patients in the N + P group (25%) and in 7 patients in the N + S group (14%). Although the incidence of ascites was similar between groups, we observed that 11 patients in the N + P group (21%) and 3 in the N + S group (6%) had clinical ascites ( $P < .04$ ); the number of remaining patients with minimal ascites was similar in both groups ( $P = NS$ ). Ascites *de novo* appeared in 10 of 13 patients in the N + P group and in 5 of 7 patients in the N + S group ( $P = NS$ ). Of the 19 patients with previous ascites, only 5 had a recurrence during the study (3 in the N + P group and 2 in the N + S group). The cumulative probabilities of patients to be free of ascites after 60 months of follow-up were 57% in the N + P group and 73% in the N + S group ( $P = NS$ ) (Fig. 2).

Considering variceal bleeding and ascites together in each group, 20 patients (39%) in the N + P group and 10 patients (20%) in the N + S group had both hypertensive complications ( $P < .04$ ).

Type of treatment, dosage of nadolol, age, sex, Child-Pugh score, cause of cirrhosis, and previous episodes of ascites did not have an independent predictive value of

**Table 3. Biochemical Parameters and Endogenous Vasoactive System Before and After Both Treatments**

	N + P (n = 51)		N + S (n = 49)	
	B	A	B	A
Hematocrit (%)	$39 \pm 5$	$38 \pm 5$	$41 \pm 5$	$40 \pm 7$
Serum albumin (g/dL)	$3.5 \pm 0.6$	$3.3 \pm 0.5$	$3.6 \pm 0.6$	$3.5 \pm 0.6$
Prothrombin index (%)	$72 \pm 17$	$72 \pm 18$	$76 \pm 18$	$80 \pm 15$
Serum bilirubin (mg/dL)	$1.4 \pm 1.1$	$1.5 \pm 1.2$	$1.3 \pm 0.7$	$1.2 \pm 0.8$
Serum creatinine (mg/dL)	$0.8 \pm 0.1$	$0.8 \pm 0.2$	$0.9 \pm 0.2$	$0.9 \pm 0.2$
Serum sodium (mEq/d)	$140 \pm 5$	$140 \pm 4$	$139 \pm 5$	$136 \pm 7$
Urinary sodium (mEq/d)	$122 \pm 75$	$114 \pm 82$	$118 \pm 61$	$122 \pm 58$
Plasma renin activity (ng/ml/h)*	$1.8 \pm 1.7$	$1.6 \pm 1.5$	$1.6 \pm 1.3$	$4.4 \pm 2.4^\dagger$
Plasma aldosterone (pg/dL)*	$87 \pm 59$	$83 \pm 48$	$79 \pm 55$	$268 \pm 216^\dagger$

Abbreviations: B, before both treatments; A, after both treatments.

\*Only measured in 12 patients in each group before and after 18 months of treatment.

$^\dagger P < .01$ .

**Table 4. Hemodynamic Effects of Nadolol or Nadolol Plus Spironolactone**

	N + P (n = 12)		N + S (n = 12)	
	Basal	2 Mo	Basal	2 Mo
HR (beats/min)	75.3 ± 19	56 ± 3*	76 ± 11	56 ± 4*
MAP (mm Hg)	87 ± 9	85 ± 8	94 ± 8	83 ± 8*
RAP (mm Hg)	3.3 ± 1.7	4.2 ± 1.9	4.9 ± 2.1	4.2 ± 2.9
PAP (mm Hg)	12 ± 4.6	14 ± 3.7	13 ± 3.3	12.6 ± 4
PCP (mm Hg)	7.8 ± 3	8 ± 2.6	7.5 ± 2.8	8.5 ± 3.1
CO (L/min)	7.3 ± 1.2	5.7 ± 1.4*	7 ± 2.6	5 ± 2.1*
SVR (dyne · s · cm <sup>-5</sup> )	930 ± 166	1,197 ± 261*	1,067 ± 358	1,388 ± 537
HVPG (mm Hg)	16.3 ± 3.7	14.3 ± 3.5*	17.9 ± 2.1	15 ± 3.3*
WHVP (mm Hg)	21.8 ± 5.7	21.3 ± 3.8	23.8 ± 3.3	21.4 ± 4.7*
FHVP (mm Hg)	5.6 ± 3	7 ± 1.2	6 ± 1.6	6.4 ± 3.3

NOTE. Four patients in the N + P group and 5 patients in the N + S group had a good HVPG response, without differences between groups.

Abbreviations: HR, heart rate; MAP, mean arterial pressure; RAP, right atrial pressure; PAP, pulmonary artery pressure; PCP, pulmonary capillary pressure; CO, cardiac output; SVR, systemic vascular resistance; WHVP, wedge hepatic venous pressure; FHVP, free hepatic venous pressure.

\* $P < .05$  vs. baseline.

bleeding when tested by Cox's multiple regression analysis.

Three patients in the N + P group and one patient in the N + S group died. A patient in the N + P group died of variceal bleeding, and the other 2 died of lung and bladder cancer, respectively. The cause of death in the patient in the N + S group was hepatic failure. The cumulative probability of survival was 91% in the N + P group and 97% in the N + S group (Fig. 3).

When the results were analyzed at a mean follow-up of  $22 \pm 16$  months, the rates of bleeding and ascites were not different between both groups of patients. Considering that the cumulative risk of bleeding and ascites was 27% and 43%, respectively, in the N + P group and 21% and 27% in the N + S group, we estimated that a sample size of 534 and 432 patients, respectively, would be necessary to achieve a statistical difference between both groups ( $\alpha = 0.05$  and  $\beta = 0.20$ ). Therefore, we decided to stop the trial because we would be unable to recruit such a number of patients.

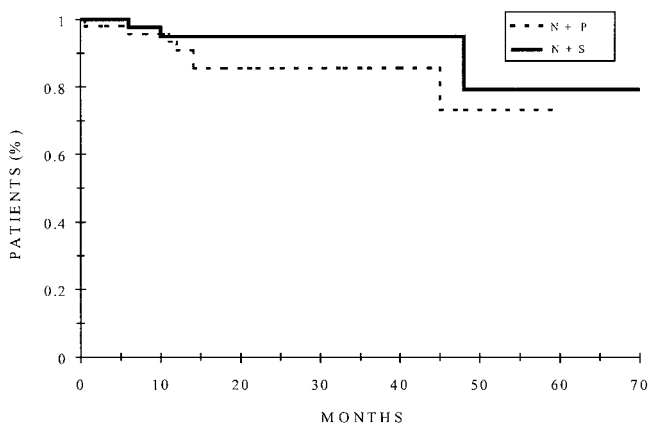


Fig. 1. Cumulative probability of being free of bleeding in the N + P and N + S treatment groups (NS).

## Discussion

Hemodynamic studies have shown that spironolactone may be effective in decreasing portal and variceal pressures.<sup>5,6,8,9</sup> However, the clinical effectiveness of nadolol plus spironolactone to protect cirrhotic patients with esophageal varices at risk for bleeding has not yet been investigated.

We report the results of the first long-term, prospective, double-blind, randomized clinical study comparing the efficacy and safety of the association of nadolol and spironolactone with nadolol alone in the prophylaxis of first variceal bleeding in nonascitic cirrhotic patients.

Taking into account that a group of patients included in this study would be treated with spironolactone, we also examined its ability to prevent the development of ascites as a secondary end point.

Previous hemodynamic studies have shown that treatment with spironolactone decreased portal and variceal pressures in human and experimental cirrhosis.<sup>5-9,15,16</sup> Moreover, the acute intravenous addition of propranolol

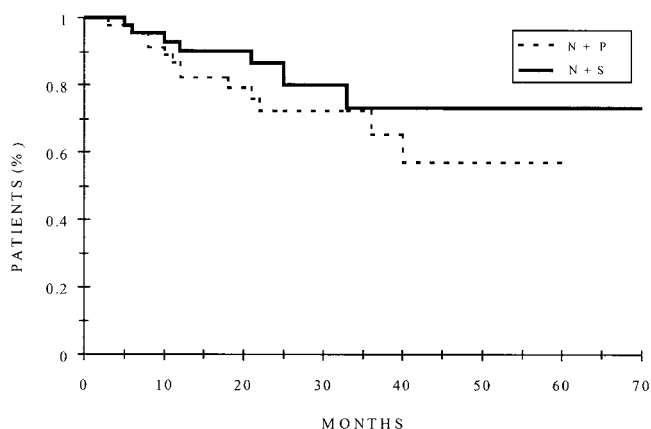


Fig. 2. Cumulative probability of being free of ascites in the N + P and N + S treatment groups (NS).

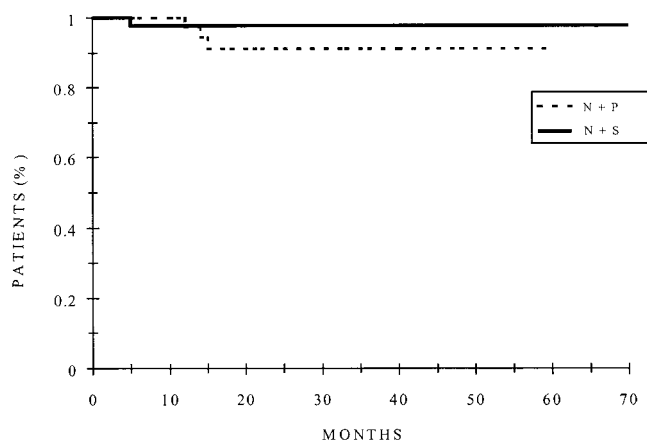


Fig. 3. Cumulative probability of survival in the N + P and N + S treatment groups (NS).

to long-term administration of spironolactone further reduces HVPG.<sup>7</sup> Nevens et al. showed that spironolactone also reduced variceal pressure in patients on long-term  $\beta$ -blocker therapy.<sup>9</sup> On the other hand, Sugano et al. did not find differences in the mean reduction of HVPG between patients treated with low-dose transdermal nitroglycerin alone or associated with spironolactone.<sup>17</sup> In the present trial, long-term administration of nadolol plus spironolactone produced a higher but not significant decrease in HVPG compared with nadolol alone (16% vs. 11.5%). This effect could be related to a decrease in effective intravascular volume suggested by the significant increases in plasma renin activity and plasma aldosterone levels observed in patients treated with the combined therapy. Another possible explanation for the reduction in HVPG could be a decrease in the intrahepatic vascular resistance produced by the calcium channel blocking action of spironolactone.<sup>12,18</sup> This probable vasodilator property of spironolactone would explain why short-term or long-term administration of furosemide did not produce any significant changes in HVPG, total blood volume, or azygos blood flow despite a decrease in cardiac output.<sup>5,19</sup>

The different results of the current trial compared with other hemodynamic studies could be attributed to the fact that our patients followed an unrestricted-sodium diet. We decided on this diet by taking into account the study design, which included patients without ascites and their poor compliance with a low-sodium diet for a long time. It had been shown in portal-hypertensive rats<sup>20</sup> and in cirrhotic patients<sup>6</sup> that restriction of sodium produces a significant reduction in plasma volume and improves the hyperdynamic circulation associated with cirrhosis. In this trial, treatment with spironolactone probably did not result in additional effects because the administered amount of sodium blunted a more pronounced decrease

of plasma volume. However, it has also been shown that spironolactone decreases portal and variceal pressures in patients following a normal-sodium diet.<sup>5,9</sup> Therefore, we believe it is unlikely that intake of sodium plays a major role in our results.

We observed a low incidence of bleeding in the whole group, particularly in patients treated with spironolactone plus nadolol. In absolute terms, only 10 patients bled and decreased almost by half in the combined treatment group (7 vs. 3). This could be related to the inclusion of patients with less severe liver disease (mean Child-Pugh score of  $5.9 \pm 1$ ) and without ascites. In this regard, it has been shown that ascites is an important prognostic factor increasing the risk of bleeding<sup>21</sup> and was the most important indicator of both bleeding and death risks in a trial comparing patients with and without ascites treated with propranolol.<sup>22</sup> Vorobioff et al. observed that, after 3 months of treatment with propranolol, portal pressure decreased significantly more often in patients without ascites than in those with ascites.<sup>23</sup> The effectiveness of propranolol in nonascitic cirrhotic patients is in keeping with a pathophysiologic study reporting that the density of  $\beta$ -adrenoreceptors in circulating mononuclear cells is reduced in patients with ascites, probably resulting in a low hemodynamic response to  $\beta$ -blockers.<sup>24</sup> This evidence suggests that  $\beta$ -blockers are more effective in reducing portal hypertension in compensated cirrhotic patients, even more when administered at early stages before the appearance of esophageal varices.<sup>25</sup>

Although the development of ascites was similar in both groups, the subset of patients with clinical evidence of this complication was significantly higher in the group treated with nadolol alone than in those who received the combined treatment. Ascites *de novo* was reduced by 50% in patients who received combined treatment compared with those treated with nadolol alone (12% vs. 25%); however, this difference was not significant. The incidence of ascites *de novo* in patients treated with nadolol alone was similar to that reported in long-term trials on primary prophylaxis of variceal bleeding with  $\beta$ -blockers ranging from 27% to 32%.<sup>22,26,27</sup> All of these findings show that a trend toward the association of nadolol and spironolactone may be useful in the prevention of clinical ascites that should be treated with sodium restriction and diuretics, whereas minimal ascites, only detectable by ultrasonography, does not necessitate specific treatment.<sup>28</sup>

A further analysis, according to the occurrence of variceal bleeding and ascites in each group of patients, showed that the incidence of both complications was significantly higher in patients treated with nadolol alone than in those treated with spironolactone plus nadolol. This interesting finding supports the concept that the

prevention of ascites would increase the efficacy of nadolol therapy.<sup>21</sup>

Although withdrawals due to adverse effects were similar in both groups, most were related to  $\beta$ -blockade rather than to spironolactone (9 vs. 2). Only 2 patients in the combined treatment group developed an increase in serum creatinine and urea levels associated, in one of the patients, with hyperkalemia that improved with discontinuation of the diuretic drug. Despite the concern that serious gynecomastia might be a problem in male patients receiving spironolactone therapy,<sup>9</sup> none of the patients in this trial had to be withdrawn for this adverse event.

In conclusion, these preliminary results suggest that nadolol plus spironolactone is not more effective than nadolol alone in preventing the first variceal bleeding in nonascitic cirrhotic patients. However, this combined treatment would prevent both complications of portal hypertension, particularly the appearance of clinical ascites. Future clinical trials with a greater number of patients will be necessary to define the role of spironolactone in the prophylaxis of the first variceal bleeding.

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