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RAPID COMMUNICATION

Hemodynamic effects of propranolol with spironolactone in patients with variceal bleeds: A randomized controlled trial

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Abstract

AIM: To study the hemodynamic effects of spironolactone with propranolol *vs* propranolol alone in the secondary prophylaxis of variceal bleeding.

METHODS: Thirty-five cirrhotics with variceal bleeding randomly received propranolol (n = 17: Group A) or spironolactone plus propranolol (n = 18: Group B). Hemodynamic assessment was performed at baseline and on the eighth day.

RESULTS: Spironolactone with propranolol caused a greater reduction in the hepatic venous pressure gradient than propranolol alone (26.94% *vs* 10.2%; $P < 0.01$). Fourteen out of eighteen patients on the combination treatment had a reduction in hepatic venous pressure gradient to $\leqslant$ 12 mmHg or a 20% reduction from baseline in contrast to only six out of seventeen (6/17) on propranolol alone ($P < 0.05$).

CONCLUSION: Spironolactone with propranolol results in a better response with a greater reduction in hepatic venous pressure gradient in the secondary prophylaxis of variceal bleeding. A greater number of patients may be protected by this combination therapy than by propranolol alone. Hence, this combination may be recommended for secondary prophylaxis in patients with variceal bleeding.

Key words: Hepatic venous pressure gradient; Secondary prophylaxis; Spironolactone; Propranolol; Variceal bleeding

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INTRODUCTION

Variceal hemorrhage is one of the serious complications of portal hypertension in cirrhotics. About 70% of the survivors of variceal bleeds re-bleed within a year[1,2]. Of the various treatment modalities, pharmacotherapy is one of the more attractive avenues, as it is simple and safe and can be applied outside the hospital.

Beta-blockers like propranolol are the treatment of choice for primary prophylaxis of variceal hemorrhage[3]. Reduction of the hepatic venous pressure gradient (HVPG) to $\leqslant$ 12 mmHg is protective, while reduction by greater than or equal to 20% of the baseline value is also safe[4,5].

However, only about one-third of patients taking propranolol alone achieve such reductions among bleeders[4-6]. Thus, a considerable number of patients are not protected by propranolol alone, particularly for secondary prophylaxis.

Hence drug combinations have been advocated for prevention of variceal re-bleeding. Recently, a combination of isosorbide mononitrate with propranolol has been tested for the prevention of variceal re-bleeding, with some benefit[7]. There have been a few studies showing efficacy of spironolactone (a drug that is commonly prescribed in cirrhotics with ascites) in the reduction of portal pressure among cirrhotics without ascites[8-11]. We evaluated the hemodynamic effects of a combination therapy of propranolol with spironolactone and found the combination had greater efficacy than propranolol alone, in propranolol-resistant cases[12]. Considering these facts, we have examined the portal hemodynamic effects of propranolol alone and propranolol in combination with spironolactone among cirrhotics who have bled at least once.

MATERIALS AND METHODS

Forty-two consecutive liver cirrhosis patients with variceal bleeding were enrolled from the Liver Clinic of Medical College and Hospital Calcutta. This study was carried out from June 2005 to March 2007. Hemodynamic studies were undertaken in the catheter laboratory of The Institute of Cardiovascular Sciences, RG Kar Medical College and Hospital, Calcutta, which is situated close to Medical College Calcutta. The institutional ethics committees of both the hospitals approved the study protocol. Only those patients who had experienced at least one episode of variceal bleeding within the previous week were considered. After admission to hospital due to upper gastrointestinal bleeding with clinical features of chronic liver disease, patients underwent upper gastrointestinal endoscopy on the following day. Those patients who came with acute bleeding were initially treated with vasoconstrictors (like terlipressin), plasma expanders or blood transfusions, as and when necessary, and endoscopy was performed twenty-four hours after their hemodynamic stabilization. In the event of re-bleeding, endoscopic banding was performed. Only those patients with evidence of active variceal bleeding or clots or oozing from the varices were included. In addition, those patients with upper gastrointestinal bleeding who had esophageal varices in the absence of any other source of upper gastrointestinal bleed were also included. Patients were excluded for any of the following reasons: Asthma, congestive cardiac failure, severe diabetes, severe hypertension, any severe co-morbid states, age less than 15 years or more than 70 years, or previous treatment with endoscopic sclerotherapy, variceal ligation, porto-systemic shunt surgeries, beta-adrenergic blocking agents, spironolactone or nitrates. The procedures to be employed were explained to the patients and, after obtaining informed written consent, patients remained hospitalized for the duration of the study. All patients underwent blood tests to evaluate the liver chemistry (liver function tests, prothrombin time) and to establish the etiology of chronic liver disease (viral markers, anti-nuclear factor, ceruloplasmin). They also underwent routine investigations (complete hemogram, urea, creatinine, random sugar, electrolytes), ultrasonography with Doppler study and liver biopsy (as and when necessary) to establish the diagnosis. Variceal grading was adopted as per the Japanese Research Society[13]. Thereafter, the patients were transferred to The Institute of Cardiovascular Sciences, RG Kar Medical College for hemodynamic assessment. The first hemodynamic study was performed within a week of the last variceal bleeding episode.

Hemodynamic study

All patients received a normal hospital diet, without any sodium restriction. Hemodynamic studies were carried out in all cases within a week of variceal bleeding after an overnight fast using a standard technique[14] in the catheter laboratory of the Institute of Cardiovascular Sciences RG Kar Medical College, Calcutta. Under local anesthesia in the supine position, a venous introducer was placed in the right femoral vein by the Seldinger technique. Under fluoroscopic guidance (Axiom Artis; Siemens, Munich Germany), a 7F balloon-tipped catheter (USCI; CR Bard Ireland, Galway, Ireland) was introduced into the main right hepatic vein through the inferior vena cava (IVC). Free (FHVP) and wedged (occluded) (WHVP) hepatic venous pressures were measured using a hemodynamic monitor (Axiom Sensis Germany) with pressure transducers (SIEMENS HEMOMED). Thereafter, we also measured the pressures in the IVC, right atrium (RA), mean pulmonary arterial pressure (MPAP) and pulmonary capillary wedge pressure (PCWP) in the similar fashion, wherever possible. Hepatic venous pressure gradient (HVPG) was calculated as the difference between WHVP and FHVP. All measurements were made in triplicate and means were obtained (data were recorded from the tracer curves).

After the baseline readings, the patients were divided into two groups by a computer-generated randomized table. One group (Group A) received propranolol (Inderal; ICI Pharmaceuticals, Chennai) at a dose of 40 mg twice daily and a placebo tablet in place of spironolactone, and the other group (Group B) received propranolol (40 mg twice daily) with spironolactone (Aldactone; 100 mg once daily; Searle: India, Mumbai). The dose of propranolol was gradually increased until a twenty percent reduction from the baseline pulse rate, or a pulse rate of 60 was achieved, which ever came earlier. Hemodynamic studies were repeated on the eight day, after the morning dose. The patients, the investigators, the cardiologist and the statistician conducting the hemodynamic study were blinded to the nature of the treatment given.

Responders were defined as those individuals showing a reduction of HVPG to $\leqslant$ 12 mmHg and/or greater than a 20% reduction in HVPG from the baseline (primary outcome)[5].

Forty-two patients with clinical features of chronic liver disease were initially considered and had upper gastrointestinal endoscopy. Of these, thirty-eight patients were considered for hemodynamic assessment. Of the four patients excluded, two had chronic obstructive lung disease, one had uncontrolled diabetes mellitus and the last was a case associated with peptic ulcer disease. Of these thirty-eight patients, thirty-five patients were included in the final analysis. Three more patients were excluded, as one of them had severe re-bleeding for which emergency endoscopic therapy was performed before hemodynamic assessment could be undertaken and the other two declined the second reading.

Statistical analysis

Results are expressed as mean ± SD. Chi-square tests, correlation and regression, paired *t* test and single factor ANOVA were used as required. $P < 0.05$ was considered statistically significant.

RESULTS

Thirty-five cirrhotics with variceal bleeding were included in the final analysis. The clinical and biochemical profiles of the included patients are given in Table 1. No subject had varices less than grade Ⅱ. Sixteen of our cases (45.71%) were alcoholics; nine (25.71%) were of viral etiology, in eight patients (22.86%) no etiology was found, and there was one each of Wilson's and autoimmune liver disease.

Table 1 Clinical and biochemical profiles of patients on propranolol or propranolol and spironolactone

Characteristics	Group A *n* = 17	Group B *n* = 18	*P* value
Male:Female ratio	12:5	15:3	
Age (yr)	44.3 ± 7.98	46.61 ± 8.71	0.09
Ascites	10	8	
Encephalopathy	1	2	
Etiology			
Alcoholic	6	10	
Hepatitis-B	6	2	
Hepatitis-C	0	1	
Others	5	5	
Varices			
Ⅱ	3	4	
Ⅲ	11	9	
Ⅳ	3	5	
Child's score			
A	3	4	
B	8	9	
C	6	5	
Bilirubin (mg/dL)	2.26 ± 1.8	2.13 ± 2.13	0.85
Albumin (mg/dL)	2.89 ± 0.46	2.71 ± 0.78	0.42
Globulin (mg/dL)	3.72 ± 0.76	4.64 ± 2.26	0.12
ALT (IU/L)	79.35 ± 75.43	43.89 ± 18.20	0.08
Urea (mg/dL)	29.53 ± 11.03	28.6 ± 13.57	0.83
Creatinine (mg/dL)	0.88 ± 0.27	0.84 ± 0.28	0.67
Na^+ (mEq/L)	135.7 ± 4.9	133.22 ± 4.61	0.13
K^+ (mEq/L)	3.74 ± 0.56	3.66 ± 0.49	0.64
Prothrombin time (INR)	1.21 ± 0.16	1.34 ± 0.40	0.30
Dose of propranolol (mg/d)	92.94 ± 23.39	88.89 ± 20.83	0.59

Values are shown as mean ± SE, $P < 0.05$ considered statistically significant. Group A: Propranolol; Group B: Propranolol and Spironolactone; ALT: Alanine aminotransferase.

There was no statistically significant difference in the clinical and biochemical profiles between Group A (only propranolol) and Group B (propranolol with spironolactone), as shown in Table 1.

In Group A, there was a significant reduction in HVPG after therapy, as compared with the baseline ($P < 0.01$, Table 2). The differences in other hemodynamic parameters before and after propranolol administration were not statistically significant. Interestingly, in Group A, there was a paradoxical rise in HVPG in 5 patients (45.45%) among the non-responders (11 patients). We also observed a rise in FHVP in 10 out of the 17 patients on propranolol.

In Group B, there were significant reductions in both WHVP and HVPG after therapy compared with the baseline ($P < 0.001$, Table 2). None of the patients showed an increase in HVPG after drug therapy in contrast to five patients in Group A. We also observed an increase in FHVP among 9 of the 18 patients on propranolol with spironolactone.

Comparing Group A with Group B, 6 of the 17 patients (35.29%) in Group A and 14 of the 18 patients (77.78%) in Group B showed an HVPG reduction to either ⩽ 12 mmHg or at least a 20% reduction from the baseline (responder) ($P = 0.011$) Interestingly, 6 of the 17 patients (35.29%) in Group A and 13 of the 18 patients (72.2%) in Group B showed a 20% reduction in HVPG from the baseline ($P = 0.0283$). Among these, 5 patients (29.41%) in Group A and 11 patients (61.11%) in Group B had an absolute reduction in HVPG to ⩽ 12 mmHg ($P = 0.0599$).

The percent reductions in HVPG from baseline after a seven-day therapy were 10.2% and 26.94% in Group A and Group B, respectively, which was also statistically significant ($P < 0.05$, Table 2).

Compared with the baseline, post-drug right atrial pressures increased significantly among the responders (5.2 mmHg *vs* 6.1 mmHg, $P < 0.05$) in contrast to the non-responders (4.73 mmHg *vs* 5.87 mmHg, $P = 0.12$).

Interestingly, analyzing the baseline hemodynamic parameters in responders, we observed a strong inverse correlation between HVPG and MPAP ($r = -0.58$) and a moderate inverse correlation between PCWP ($r = -0.48$) and RA pressures ($r = -0.30$). However after drug treatment, these relationships ceased to exist. By contrast, among non-responders, no correlation was observed between the baseline HVPG and any of MPAP ($r = -0.141$), PCWP ($r = -0.069$) and RA pressures ($r = -0.0007$).

DISCUSSION

For pharmaco-prophylaxis of variceal bleeding, most drugs act by vasoconstriction to reduce portal pressure. Increased blood volume, a common feature in decompensate cirrhosis, has a contributory effect in increasing portal pressure. It has been found acute expansion of blood volume by transfusion increases the chances of re-bleeding in a bleeder[15]. Moreover, increased blood volume maintains the hyper dynamic state of portal hypertension[16]. Thus, a reduction in plasma volume may reduce portal pressure. Spironolactone, a mineralocorticoid-blocking agent is used for its ability to reduce portal pressure as measured by HVPG[8-10]. Thus, the combination of spironolactone with a beta-blocker may reduce the portal pressure in a better way. The rationality behind the use of combination therapy is that effects acting through different mechanisms may be additive or even synergistic[17].

In this study, a significantly larger number of patients responded to combination therapy than responded to propranolol alone (14/18 *vs* 6/17, $P < 0.05$).

A better response with spironolactone was observed in a subset of eight non-ascitic patients who did not respond to propranolol for primary prophylaxis[11]. Variceal pressure was measured by endoscopy in that study. We also observed in our previous study that spironolactone when combined with propranolol reduced portal pressure in propranolol-resistant cases (measuring HVPG)[12].

Studies have shown spironolactone does not further reduce portal pressure in patients already on low-dose transdermal nitroglycerine[18] or beta-blockers like nadolol[19] for primary prophylaxis.

The most important observation in our study is the significantly larger number of patients on combination therapy showing either an absolute reduction in HVPG to ⩽ 12 mmHg or at least a 20% reduction from the baseline (responder) compared with those on propranolol alone ($P = 0.011$).

A landmark paper by Feu *et al*[5] observed for the first time that a reduction in HVPG of more than 20% of

Table 2 Hemodynamic parameters at baseline and on d 8 of therapy

Characteristics	Group A (n = 17)			Group B (n = 18)			Group A *vs* Group B *P*-value	
	Baseline	d 8	*P*-value	Baseline	d 8	*P*-value	Baseline	d 8
Pulse rate (/min)	86.80 ± 12.0	69.17 ± 8.66	0.058	79.89 ± 10.21	64.66 ± 8	0.00003	0.08	0.12
SBP (mmHg)	123.88 ± 11.82	117.41 ± 9.45	0.0003	123.76 ± 11.3	118.44 ± 8.85	0.001	0.98	0.74
IVCP (mmHg)	7.29 ± 3.33	7.19 ± 2.95	0.89	7.33 ± 3.6	7.11 ± 3.34	0.74	0.97	0.95
FHVP (mmHg)	7.88 ± 3.12	8.82 ± 3.99	0.28	8.22 ± 3.64	9.00 ± 3.14	0.25	0.76	0.86
WHVP (mmHg)	24.65 ± 3.23	23.88 ± 5.11	0.54	24.56 ± 4.3	20.78 ± 3.83	0.00009	0.94	0.052
HVPG (mmHg)	16.76 ± 2.66	15.06 ± 4.35	0.04	16.11 ± 1.97	11.78 ± 2.07	-	-	-
RAP (mmHg)	4.88 ± 2.87	6.25 ± 2.57	0.007	5.11 ± 2.59	5.78 ± 2.39	0.27	0.81	0.58
MPAP (mmHg)	17.46 ± 3.91	19.58 ± 4.8	0.32	18.11 ± 4.43	18.80 ± 4.29	0.60	0.76	0.82
PCWP (mmHg)	14.54 ± 6.78	14.33 ± 6.82	0.94	15.50 ± 4.53	14.40 ± 4.95	0.48	0.69	0.98

All the values are shown as mean ± SE. $P < 0.05$ considered statistically significant. SBP: Systolic blood pressure; IVCP: Inferior vena cava pressure; FHVP: Free hepatic venous pressure; WHVP: Wedge hepatic venous pressure; HVPG: Hepatic venous pressure gradient; RAP: Right atrial pressure; MPAP: Mean pulmonary artery pressure; PCWP: Pulmonary capillary wedge pressure; Group A: Propranolol; Group B: Propranolol and Spironolactone.

baseline, even if not reaching the 12 mmHg target, is associated with almost complete protection against variceal re-bleeding. Eight studies[5,20-26], either RCTs or prospective consecutive series, have shown the pharmacologic (or spontaneous) reduction of HVPG to less than 12 mmHg, or by as much as or more than 20% of the baseline value, virtually abolishes the risk of re-bleeding.

As mentioned earlier, one study demonstrated that addition of isosorbide mononitrate improved the efficacy of propranolol in the prevention of variceal re-bleeding on long-term follow up[7].

The combination of spironolactone with propranolol showed a significantly greater percent reduction of HVPG from the baseline, as compared with propranolol alone (26.94% *vs* 10.2, $P < 0.05$). This greater reduction in HVPG with combination therapy may in part be explained by a paradoxical rise in FHVP with a concomitant significant reduction in WHVP, in contrast to only a rise in FHVP without a significant post treatment reduction in WHVP in patients on propranolol alone. However, propranolol alone also significantly reduced HVPG from the baseline after 7-d therapy ($P < 0.05$).

Since ascites does not alter HVPG or the gradient between portal venous pressure and intra-abdominal pressure[27,28], reduction of HVPG by the addition of spironolactone is likely to be due to a true reduction in portal venous pressure and not due to a reduction in intra-abdominal pressure consequent to control of the ascites. Moreover, spironolactone, by reducing plasma volume, may reduce both WHVP and FHVP; thus, it should not influence HVPG. The efficacy of spironolactone in the reduction of portal pressure in patients without ascites has already been demonstrated[17]. Reduction of plasma volume and associated vasoactive mechanism may underlie the effects of spironolactone on portal pressure[11]. However, some evidence suggests spironolactone may have a direct effect on the vasculature, independent of its anti-aldosterone effect[29]. Spironolactone also has a unique property of inhibition of hepatic stellate cell activation and Na/H exchange isoform-1 (NHE-1) protein expression[30]. Spironolactone was shown to have a mineralocorticoid receptor-independent suppressive effect on immuno-active and inflammatory cytokines[31]. An anti fibrotic property has also been evidenced experimentally in rats[30]. Recent studies have also demonstrated the aldosterone antagonist eplerenone prevents epithelial cell growth and stiffening of venous and arterial endothelia[32].

Although most studies evaluated the effects of spironolactone over a longer period of time (4-8 wk), we completed our second hemodynamic reading after a week, considering that chance of re-bleeding after the index bleeding is maximal during the first two weeks. Moreover, one of the major active metabolites of spironolactone is canrenone, which has a slow clearance and a half-life of 10-35 h. Thus, to reach a steady state plasma concentration it would take a period of between 2-7 d.

Incidentally we observed a significant rise in right atrial pressures only among the responders of both groups following drug therapy. Moreover, there was a moderate to strong inverse correlation between the baseline HVPG and the baseline MPAP, PCWP and RA pressures, only among the responders. The significance or role of this observation needs further evaluation.

Hence, spironolactone, a drug commonly prescribed in cirrhotics for the reduction of ascites, has a potential independent portal pressure-reducing effect, and its impressive reduction of HVPG in combination with propranolol may pave our way to recommend this combination for secondary prophylaxis in variceal bleeding.

COMMENTS

Background

Variceal bleeding is one of the potentially life threatening complications of portal hypertension. About 70% of the survivors of variceal bleeds re-bleed within one year. Beta-blockers like propranolol have been the treatment of choice for prevention of variceal bleeding. However, only about one-third of the patients taking propranolol achieve a significant reduction in the hepatic venous pressure gradient to be considered risk free. Hence, drug combinations have been advocated for the prevention of variceal bleeding.

Research frontiers

Various drug combinations have been tested for the prevention of variceal bleeding; for example, propranolol with isosorbide mononitrate. However, the problem with drug combinations is an increased incidence of side effects, which leads to discontinuation of therapy. The challenge is to find a drug combination that is not only effective but also safe and easy to administer over long periods of time.

Innovations and breakthroughs

Spironolactone, a drug commonly used in cirrhotics with ascites to reduce fluid overload, has been found to have an independent portal hypotensive effect. The drug has been in use for a long period of time and has been found to be safe and free of side effects except for occasional gynaecomastia. The idea was to study the hemodynamic changes induced by the combination of spironolactone with propranolol, and compare it with propranolol alone, the gold standard drug. The significantly better response of patients receiving this combination pharmacotherapy (spironolactone plus propranolol) for secondary prophylaxis of variceal bleeding may be considered as a breakthrough.

Applications

We found the combination of spironolactone with propranolol resulted in a significantly greater reduction in HVPG than propranolol alone, and this reduction was significant enough to cause patients to be relatively risk free from recurrence of variceal bleeds. However, long-term prospective studies are needed in a larger number of patients to actually observe the recurrence of variceal bleeding, if any.

Terminology

The hepatic venous pressure gradient (HVPG) is measured by the introduction of a balloon-tipped catheter into the hepatic vein. HVPG is a very strong marker of the degree of portal hypertension.

Peer review

This is a very interesting study dealing with a significant clinical problem. It is well conducted and most significant issues are addressed.

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