

## Effects of propranolol or propranolol plus isosorbide-5-mononitrate on variceal pressure in schistosomiasis

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### Abstract

**AIM:** To compare the effects of propranolol (PR) to that of PR plus isosorbide-5-mononitrate (ISMN) on variceal pressure in patients with schistosomiasis.

**METHODS:** Forty-eight patients with schistosomiasis

who had no previous variceal bleeding were treated with PR alone or PR plus ISMN. Seven patients refused variceal pressure manometry (3 receiving PR and 4 receiving PR plus ISMN). One patient withdrew from the trial due to headache after taking ISMN. At the time of termination, twenty patients were randomly assigned to treatment with PR plus ISMN or PR alone. The dose of PR was adjusted until the resting heart rate had been reduced by 25% or was less than 55 bpm. In the PR plus ISMN group, after PR was titrated to the same target, the dose of ISMN was increased up to 20 mg orally twice a day. Variceal pressure was measured using a noninvasive endoscopic balloon technique at the end of the 6-mo treatment period.

**RESULTS:** In 40 patients (20 in the PR group and 20 in the PR plus ISMN group), variceal pressure was measured before treatment and at the end of the 6-mo treatment period. PR or PR plus ISMN treatment caused a significant reduction in variceal pressure (PR group: from  $24.15 \pm 6.05$  mmHg to  $22.68 \pm 5.70$  mmHg,  $P = 0.001$ ; PR plus ISMN group: from  $25.69 \pm 5.26$  mmHg to  $20.48 \pm 5.43$  mmHg;  $P < 0.001$ ). The percentage decrease in variceal pressure was significant after PR plus ISMN compared with that after PR alone ( $15.93\% \pm 8.37\%$  vs  $6.05\% \pm 3.67\%$ ,  $P = 0.01$ ). One patient in the PR plus ISMN group and two patients in the PR group had variceal bleeding during follow-up. There were no significant differences between the two groups regarding the incidence of variceal bleeding. In the PR plus ISMN group, three patients had headache and hypotension. The headache was mild and transient and promptly disappeared after continuation of the relevant drug in two patients. Only one patient withdrew from the trial due to severe and lasting headache after taking ISMN. No side effects occurred in the PR group.

**CONCLUSION:** PR plus ISMN therapy may be an alternative treatment for patients with schistosomiasis who have a high risk of bleeding.

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**Key words:** Esophageal varices; Schistosomiasis; Portal hypertension; Bleeding; Propranolol; Variceal pressure; Isosorbide-5-mononitrate

**Core tip:** The results of the present study suggested that the combination of propranolol and isosorbide-5-mononitrate was more effective than propranolol alone in decreasing variceal pressure. This drug combination will reduce the rate of bleeding in patients with schistosomiasis, high-risk esophageal varices and no previous history of variceal bleeding.

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## INTRODUCTION

Variceal bleeding is the most frequent and severe complication of portal hypertension in patients with cirrhosis. Identification of those who have a high risk of variceal hemorrhage is effective for preventive therapy in patients with a high disease predisposition<sup>[1]</sup>. Variceal size and the red color sign are considered to be the most important endoscopic parameters in predicting variceal bleeding<sup>[2]</sup>. However, endoscopic findings alone can not be used to reliably predict the risk of variceal bleeding. The formation of esophageal varices depends on an elevation in portal pressure; a hepatic venous pressure gradient (HVPG) greater than 10 mmHg is necessary for the development of and bleeding from esophageal varices<sup>[3-6]</sup>. On the other hand, a more rational approach would be to guide pharmacologic therapy based on hemodynamic response, defined as a decrease in HVPG to < 12 mmHg or a decrease of > 20% from baseline levels<sup>[7]</sup>. However, limitations to the generalized use of HVPG measurement are the lack of local expertise and poor adherence to guidelines that will ensure reliable and reproducible measurements, and its invasive nature<sup>[5]</sup>. In the majority of published studies, the dose of nonselective  $\beta$ -blockers was titrated to decrease the heart rate by 25% from baseline or maximal tolerated doses<sup>[5,7]</sup>.

Propranolol (PR) or isosorbide-5-mononitrate (ISMN) is effective in preventing the first variceal bleeding in patients with cirrhosis<sup>[1,5]</sup>. ISMN enhances the reductive effect of PR on variceal pressure in cirrhotic patients<sup>[1,5]</sup>. In contrast to liver cirrhosis, published data regarding the effect of PR on schistosomiasis-related portal hypertension are scarce and contradictory, and the effect of ISMN plus PR treatment is unknown in these patients<sup>[8,9]</sup>. A short-term study in patients with schistosomiasis and previous variceal bleeding after PR treatment found that the portal

pressure was not decreased<sup>[8]</sup>. Moreover, the required mean dose to achieve a 20%-25% reduction in heart rate from baseline was up to 400 mg/d<sup>[8]</sup>. Cohort studies indicated that PR treatment achieved a reduction in rebleeding rates and increased the survival of patients with no serious side effects<sup>[9]</sup>. Recently, a study from Brazil found that PR significantly reduced variceal pressure in schistosomiasis patients who had never bled<sup>[10]</sup>. However, it is not clear whether ISMN plus PR is better than PR alone in the treatment of schistosomiasis patients who had never bled. In this study, we will ascertain whether the combination of PR and ISMN is more effective than PR alone in decreasing variceal pressure.

## MATERIALS AND METHODS

### Selection of patients

From September 2007 to October 2010, patients admitted to our hospital due to schistosomiasis-related portal hypertension were assessed for inclusion in the trial. The diagnosis of schistosomiasis was established in accordance with the World Health Organization criteria<sup>[11]</sup>. The eligibility criteria were age between 18 and 65, schistosomiasis eggs in stool specimens, the characteristic ultrasound criteria, and endoscopic evidence of esophageal varices. The exclusion criteria were previous treatment for portal hypertension (*e.g.*, beta-blockers, sclerotherapy, or endoscopic band ligation), severe hepatic disease (*e.g.*, Child-Pugh score higher than 12 points or hepatorenal syndrome), previous variceal bleeding, presence of any neoplastic disease, portal vein thrombosis, inability to attend follow-up, contraindications to beta-blockers (severe chronic pulmonary obstructive disease, asthma, severe insulin-dependent diabetes mellitus, heart failure, grade II atrioventricular block, sinus bradycardia < 50 bpm, aortic stenosis, peripheral arterial disease, arterial hypotension with systolic pressure < 85 mmHg), or long-acting nitrates (glaucoma). The study was approved by the Ethics Committee of Anhui Medical University, and all patients gave written informed consent to participate in the study. Patients were assigned to one of two treatment groups according to the sequential method of randomization.

### Treatment

Patients who fulfilled the inclusion and exclusion criteria were immediately randomized into the two treatment groups using consecutively numbered envelopes that contained the treatment assignments, which were generated by a system using computer-allocated random digit numbers. PR was given orally at an initial dose of 20 mg 3 times daily. The dose was subsequently adjusted over a period of 5 d until the resting heart rate had been reduced by 25% or was less than 55 bpm. In the PR plus ISMN group, after PR was titrated to the same target in resting heart rate, the dose of ISMN was increased up to an oral dose of 20 mg twice a day.

### Methods

Measurement of variceal pressure was performed after

**Table 1** Demographic profile of the study population

	PR group ( <i>n</i> = 20)	PR + ISMN group ( <i>n</i> = 20)	<i>P</i> value
Sex			0.619
Male	12	11	
Female	8	9	
Age (yr)	47.87 ± 15.16	44.14 ± 9.51	0.585
Child-Pugh grade			1.000
A	9	8	
B	11	12	
Child-Pugh score	8.87 ± 1.88	8.00 ± 1.63	0.358
Albumin (g/L)	30.63 ± 3.82	33.34 ± 5.30	0.271
Total bilirubin (μmol/L)	29.45 ± 17.02	25.11 ± 11.26	0.577
Prothrombin time (s)	16.80 ± 1.82	16.65 ± 1.59	0.875
VP (mmHg)	24.15 ± 6.05	25.69 ± 5.26	0.248
Varix grade			0.608
F2	10	9	
F3	10	11	
Red color signs	12	14	1.000

VP: Variceal pressure; PR: Propranolol; ISMN: Isosorbide-5-mononitrate.

an overnight fast during upper gastrointestinal endoscopy. Variceal pressure was assessed with a previously described noninvasive technique using an esophageal variceal manometer (EVM; Esophageal Varix Manometer; Treier Endoscopic AG, Beromünster, Switzerland) and recorded by the workstation which was developed by our group<sup>[12,13]</sup>. To minimize esophageal tonus and peristalsis, all patients received premedication with 5 mg diazepam and 20 mg *n*-butylscopolamine intravenously. The reliability of the endoscopic measurement of variceal pressure was determined in a previous study which found a good correlation with needle puncture measurement<sup>[13-15]</sup>. In the current study, endoscopic measurement of variceal pressure was used because of the unique hemodynamic pattern of pre-sinusoidal portal hypertension. The largest varix situated above the cardia was chosen for measurement of variceal pressure. The pressure in each patient was measured five times. Variceal pressure was calculated as the mean of five satisfactory measurement periods recorded.

After variceal pressure measurement, the size of the varix was estimated in the absence of peristaltic waves, by comparing the varix with the scales in the balloon variceal markers (5-mm intervals). The maximal size of the varices and the red color signs were recorded as proposed by the Japanese Research Society for portal hypertension<sup>[16]</sup>.

### Follow-up and endpoints

All patients were followed in the outpatient clinics at 3-month intervals and assessed for adverse events, compliance (direct questioning, prescription renewal, and reinforcement), variceal bleeding, and progression of liver disease. Variceal pressures in all patients were measured before and after 6 mo of continuous PR or PR plus ISMN therapy. The primary end point was variceal bleeding and secondary end points were treatment-related complications and mortality. Variceal bleeding was

defined as hematemesis or melena, with an associated drop in hematocrit by 10%, in the absence of any other source of gastrointestinal bleeding on endoscopy. In the case of variceal bleeding, physicians were free to choose endoscopic treatment to prevent rebleeding.

### Statistical analysis

Statistical analyses were performed with SPSS (version 10; SPSS, Inc., Chicago, IL, United States). All quantitative data were tested for normal distribution. Quantitative data were expressed as mean ± SD if the data were normally distributed. Each continuous parameter was analyzed with the independent-samples *t*-test. The paired-samples *t*-test was used to examine change from baseline to follow-up. Categorical data were examined using Fisher's exact test. *P*-values < 0.05 were considered statistically significant.

## RESULTS

### Baseline data

Twenty-five patients received PR plus ISMN and 23 patients received PR alone (dosage of PR: 60 to 160 mg/d, median: 80 mg; dosage of ISMN: 20 mg/d). Seven patients refused to variceal pressure manometry (3 receiving PR and 4 receiving PR plus ISMN). One patient withdrew from the trial due to headache after taking ISMN. Therefore, there were 20 patients in each treatment group. Clinical and endoscopic data of the patients in the subsets are shown in Table 1. There were no significant differences between the two groups at baseline with regard to clinical and demographic characteristics or baseline variceal pressure (Table 1, PR group = 24.15 ± 6.05 mmHg; PR plus ISMN = 25.69 ± 5.26 mmHg).

### Changes in variceal pressure

In 40 patients (20 in the PR group and 20 in the PR plus ISMN group), variceal pressure was measured again the end of a 6-mo continuous treatment period. PR or PR plus ISMN caused a significant reduction in variceal pressure (PR group: from 24.15 ± 6.05 mmHg to 22.68 ± 5.70 mmHg, *P* = 0.001; PR plus ISMN group: from 25.69 ± 5.26 mmHg to 20.48 ± 5.43 mmHg; *P* < 0.001). The percentage decrease in variceal pressure after PR plus ISMN was more significant than that after PR alone (Table 2, 15.93% ± 8.37% *vs* 6.05% ± 3.67%, *P* = 0.01).

### Bleeding

One patient in the PR plus ISMN group and two patients in the PR alone group had variceal bleeding during the 6-mo follow-up period. There were no significant differences between the two groups regarding the incidence of variceal bleeding.

### Adverse effects

In the PR plus ISMN group, three patients had headache and hypotension. The headache was mild and transient and promptly disappeared after continuation of the rel-

**Table 2** Effects of propranolol and propranolol plus isosorbide-5-mononitrate on variceal pressure, liver function and systemic hemodynamics in patients with 6 mo of follow-up

	PR		PR + ISMN	
	Baseline	6 mo	Baseline	6 mo
(ΔVP)%	0	15.93 ± 8.37	0	6.05 ± 3.67 <sup>a</sup>
ALB (g/L)	30.63 ± 3.82	31.14 ± 3.08	33.34 ± 5.30	34.30 ± 5.09
TB (umol/L)	29.45 ± 17.02	27.26 ± 12.27	25.11 ± 11.26	26.74 ± 12.96
SBP (mmHg)	132 ± 20	124 ± 21 <sup>d</sup>	130 ± 19	125 ± 19 <sup>d</sup>
DBP (mmHg)	77 ± 10	72 ± 11 <sup>d</sup>	74 ± 10	70 ± 13 <sup>d</sup>

<sup>a</sup>*P* < 0.05 *vs* PR group, <sup>d</sup>*P* < 0.01 *vs* baseline. (ΔVP)%: Percentage difference in variceal pressure from baseline; PR: Propranolol; ISMN: Isosorbide-5-mononitrate; ALB: Albumin; TB: Total bilirubin; SBP: Systolic blood pressure; DBP: Diastolic blood pressure.

evant drug in two patients. One patient withdrew from the trial due to severe and lasting headache after taking ISMN. No side effects occurred in the PR group. There was no worsening of liver function or impairment of renal function in the 2 groups within the 6-mo treatment period (Table 2).

## DISCUSSION

Nonselective  $\beta$ -blockers are the most commonly used drugs to prevent variceal bleeding in patients with cirrhosis and esophageal varices<sup>[6,14]</sup>. Although many trials have shown that variceal hemorrhage risk was reduced with  $\beta$ -blockers, these drugs do not protect all treated patients, probably due to an inadequate decrease in the HVP<sup>[5,17]</sup>. Most published studies have shown that PR and ISMN have a synergistic effect on reducing portal pressure and a combination of the two could be more effective than PR alone<sup>[17,18]</sup>. Recently, PR was found to significantly reduce variceal pressure and wall tension in patients with schistosomiasis<sup>[10]</sup>. However, it is uncertain whether the combination of PR and ISMN is more effective than PR alone in decreasing variceal pressure in schistosomiasis patients who have never bled.

This study investigated the efficacy of PR compared with PR plus ISMN in schistosomiasis patients that had never bled. Our approach was to assess variceal pressure in patients with high-risk varices, using the same methodology reported for cirrhotic patients<sup>[12]</sup>. Variceal bleeding is believed to occur when the tension exerted over the thin wall of the varices increases beyond a critical value determined by the elastic limit of the vessel<sup>[5]</sup>. Variceal pressure and size are key factors determining variceal wall tension. Not only is variceal pressure the best parameter for predicting rupture of varices and consequent complications, but it is also a useful guide for studying the effect of the pharmacotherapy of portal hypertension and a measure of the effects of transjugular intrahepatic portosystemic shunting<sup>[6,19-21]</sup>. As confirmed by one study, the measurement of variceal pressure can efficiently monitor the direct effect of the prophylaxis of variceal bleeding compared with the rate of bleeding in cirrhotic

patients<sup>[17]</sup>.

In the present study, we observed that PR and PR plus ISMN administration caused a significant reduction in variceal pressure in patients with schistosomiasis. After a 6-mo continuous treatment period, the percentage decrease in variceal pressure was more obvious in patients receiving PR plus ISMN than PR alone ( $15.93\% \pm 8.37\%$  *vs*  $6.05\% \pm 3.67\%$ , *P* = 0.01). Thus, the results of our study suggest that PR plus ISMN is superior to PR alone in reducing variceal pressure in patients with schistosomiasis. These results are consistent with the data from different randomized clinical trials which show that the effect in patients treated with combined pharmacological therapy was greater than that obtained with PR alone<sup>[17,18]</sup>. Therefore, the pharmacological therapy of choice in the prevention of variceal bleeding is probably the combination of PR and ISMN.

The mean dosage of PR used in our study was lower than that in other studies for cirrhotic patients and schistosomiasis patients<sup>[1,5]</sup>. However, the low dosage of PR in the current study was expected because it is well known that the metabolism of this drug is different between Asian and European patients<sup>[22]</sup>. In a previous study, Lay *et al.*<sup>[23]</sup> found that the mean daily dosage of PR was  $68.2 \pm 32.8$  mg, which was sufficient to reduce the heart rate by 25%. Therefore, it is possible that a lower dosage of PR to reach a target heart rate reduction of 25% would have enough power to result in a lower bleeding rate in a Chinese population.

Three patients treated with PR plus ISMN experienced side effects. Most reported side effects caused by  $\beta$ -blockers (hypotension, tiredness, breathlessness, poor memory, insomnia) can be easily managed by adjusting the dose of the medication, which does not affect the treatment effect. ISMN may increase vasodilatation leading to more side effects such as headache and hypotension<sup>[1,5]</sup>. In a trial performed in patients with cirrhosis and ascites which compared  $\beta$ -blockers with ISMN, the latter medication was associated with more side effects<sup>[24]</sup>. Furthermore, other studies also found a trend toward more side effects requiring withdrawal of the combination therapy compared with PR alone<sup>[17,18,25]</sup>. In our study, two patients experienced mild and transient headache on the first administration of ISMN, which disappeared after continuation of the relevant medication. One patient withdrew from the trial due to severe and lasting headache after taking PR plus ISMN. When the resting heart rate was reduced by 25% or was less than 55 bpm, most patients showed a significant reduction in variceal pressure ( $15.93\% \pm 8.37\%$ ) after receiving PR plus ISMN.

We are aware of the limitations of the current study. First, we found that the measurement of variceal pressure is technically difficult and time consuming in patients with small varices, which may reduce the applicability of measurements in clinical practice. However, because very large varices and red color signs indicate imminent bleeding, these patients are at high risk of bleeding and require prophylactic measures even though their variceal pressure



is not high<sup>[26,27]</sup>. On the other hand, the measurement of variceal pressure is probably not very important in patients with very small varices due to rare bleeding<sup>[28-31]</sup>. Second, patients not suitable for PR plus ISMN therapy need to be investigated in future studies. Third, future randomized controlled studies with a larger number of patients are warranted to confirm these findings and to demonstrate the long-term decrease in the frequency of bleeding episodes and mortality.

In conclusion, we found that combination treatment with PR plus ISMN compared with PR alone, more effectively decreased variceal pressure in schistosomiasis patients. Future randomized controlled studies with a larger number of patients are warranted to demonstrate the long-term decrease in variceal pressure, to determine when side effects will outweigh the benefits, and monitor the frequency of bleeding episodes and mortality.

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## COMMENTS

### Background

Non-cirrhotic portal hypertension and gastrointestinal bleeding are complications of the infection caused by the intravascular parasitic trematode *Schistosoma mansoni*. The prophylactic treatment of variceal bleeding is therefore crucial in the management of these patients.

### Research frontiers

Treatment with propranolol plus isosorbide-5-mononitrate resulted in a synergistic decrease in variceal pressure compared with propranolol alone in cirrhotic patients. However, this has not been demonstrated in non-cirrhotic portal hypertension caused by *Schistosoma mansoni* infection.

### Innovations and breakthroughs

In this study, the authors found that the combination of propranolol and isosorbide-5-mononitrate was more effective than propranolol alone in decreasing variceal pressure, which is important in reducing the rate of bleeding in patients with schistosomiasis, high-risk esophageal varices and no previous history of variceal bleeding.

### Applications

The results suggest that the combination of propranolol plus isosorbide-5-mononitrate should be recommended as the first prophylaxis of variceal bleeding in non-cirrhotic portal hypertension caused by *Schistosoma mansoni* infection. Additional studies with long-term follow-up are needed to confirm the results concerning mortality.

### Peer review

The authors have compared the effect of propranolol alone with the combination of propranolol and isosorbide-5-mononitrate on variceal pressure in patients with portal hypertension due to schistosomiasis. The results suggested that the combination led to a more pronounced decrease of variceal pressure than propranolol did.

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