Effect of Nitroglycerin Administration on Portal Blood Flow in Patient with Liver Cirrhosis

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Summary: *Current interest in the pharmacological manipulation of portal blood flow on the nitroglycerin. We used pulsed doppler ultrasonography to assess the effects of nitroglycerin. The measurement of the portal blood flow and velocity, heart rate, blood pressure were made at 0, 15, 30, 45 and 60 minutes (min) after administration of nitroglycerin (25μg/min) or saline (0.02 ml/min) for 15 min. Intravenous administration of nitroglycerin markedly reduced the portal blood velocity and flow, sistolic and diastolic blood pressure, increased heart rate when to compare with saline infusion group. In the nitroglycerin group portal blood velocity fell by 22-25 % ($p<0.01$), systolic and diastolic blood pressure by 16-18 % ($p<0.05$) and 9-12% ($p<0.05$), the heart rate increased by 15-18% ($p<0.05$) in between 5-60 min respectively.*

In conclusion, in this study clearly has demonstrated that an iv. administration of nitroglycerin results in a significant reduction in portal blood, flow systolic and diastolic pressure and increasing heart in patient with cirrhosis of the liver.

Key Words: Nitroglycerin, portal velocity, portal blood flow, liver cirrhosis

Bleeding from oesophageal varices is a serious complication of portal hypertension. The mortality of the first bleed, even when actively treated in specialised units is approximately 30%, (1,2) and may be considerably more in other centres. One of the most demanding aspects of treatment is the arrest of active variceal bleeding. However we have examined a new approach to this difficult clinical problem.

Up to now, the pharmacological treatment of portal hypertension has been based on the use of vasoactive drugs that reduce pressure and blood flow within the portal venous system, such as vasopressin (3), somatostatin (4) and propranolol (5,6).

A different approach may be the use of pharmacological agents that decrease the portal blood flow.

Nitroglycerin is a potent vascular dilator with a predominant effect on the venous system and a lesser effect on the arterial circulation; it acts at specific nitrate receptors in the vascular smooth muscle wall to trigger vasculer relaxation (7).

Recent studies have motivated an interest in the use of nitroglycerin in patients with cirrhosis and portal hypertension.

The drug has been shown to produce a significant decrease in portal vein pressure when infused intravenously (8,9).

The pulsed Doppler system combined with B-mode scan ultrasonography offers the advantages being less invasive, was recently intraduced, and physiologic measurements of portal blood flow have become (10-12). This study is intended to evaluate the effect of acute nitroglycerin administration on portal blood flow

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Table I: Clinical features of the patients.

Clinical features	No
Patient	7
Sex M/F	5/2
Age (yr)	
Range	42-67
Mean	52±8
Varices	
F_1	4
F_2	3
F_3	0
Child	
A	0
B	1
C	6

F_1: Straight
F_2: Enlarged tortuous
F_3: Largest

measured by the pulsed Doppler system in cirrhotic patients with portal hypertention.

MATERIAL and METHODS

Seven adult patients with portal hypertension were assessed (Table 1). In all of these patients, the primary disease was liver cirrhosis, and esophageal varices were noted endoscopically in most. Details such as age, sex are shown in table 1.

All patients were aged between 42 and 67 years and had been haemodynamically stable for at least 7 days prior to the study. The patients with a history of cardiac disease, diabetes mellitus or renal disease, and those taking vaso-active drugs, were excluded.

The patients were assessed by full physical examination, urinalysis and measurement of full blood count; coagulation screen; liver function tests, and plasma protein, gamma glutamyl-transferase and cholesterol levels. Chest x-ray and 12-lead electrocardiograph were performed.

Measurement of portal blood flow and haemodynamic variables. Portal vein anatomy and Doppler flow factors were evaluated by means of a system that combined an ultrasonic sector scanner with a 3.5-MHz transducer and a pulsed Doppler apparatus (Toshiba SAL-50A). Patients fasted overnight before the study. All measurements were performed while patients were lying quietly in a prone position and holding their breath in maximal expiration. Portal vein diameter and the angle between the Doppler beam and the long axis of the portal vein were measured from a B-scan image showing beam direction with the portal vein in its long axis. An anterior subcostal approach that provides optimal visualization of the portal vein walls was used because it provides axial resolution for a more accurate diameter measurement. Portal vein diameter was measured at a location 1 to 2 cm proximal to its bifurcation, assuming that at this site the elliptic shape of the portal vein converges towards a circle (10).

Doppler signals were obtained from a sample volume located at the centre of the portal vein. After the maximal portal vein diameter and highest mean velocity were recorded, the portal blood flow rate was obtained by multiplying the blood velocity by the cross-sectional area of the vessel, calculated on the basis of the inner diameter, assuming circular geometry (10,11).

Interobserver variations in portal blood velocity measurements were always lower than 10%. The average estimated portal blood flow rate varied always within 10%.

After an overnight fast, mean volume of portal blood flow and haemodynamic variables were measured in all patients, and subsequent 25 μg/min nitroglycerin (ADEKA, Samsun Turkey) or 0.02 ml/min saline was administered intravenously for 15 min. Maximal diameter of the portal vein, portal blood velocity, portal

Table II: The measurement of portal velocity, heart rate, blood pressure were made after administration of SMS 201-995 or saline.

Time (min)	Treatment	SBP	DBP	Pulse	Velocity
0.min	S	155±10	80±5	84±10	0.161±0.02
	NG	116±12	78±4	84±8	0.164±0.03
	%				
	P	NS	NS	NS	NS
5.min	S	118±10	77±1	82±8	0.162±0.02
	NG	98±11	70±2	96±9	0.125±0.02
	%	16.9	9	17	22.8
	P	<0.05	<0.05	<0.05	<0.01
15.min	S	114±10	80±4	83±8	0.159±0.03
	NG	95±9	72±3	99±10	0.120±0.02
	%	16.9	10	18	24.5
	P	<0.05	<0.05	<0.05	<0.01
30.min	S	116±9	77±5	85±9	0.163±0.03
	NG	95±8	69±4	98±6	0.115±0.03
	%	18	10.3	15.2	29.4
	P	<0.05	<0.05	<0.05	<0.01
45.min	S	119±8	80±6	84±8	0.164±0.03
	NG	99±10	70±5	97±8	0.119±0.02
	%	16.8	12.5	15.4	27.4
	P	<0.05	<0.05	<0.05	<0.01
60.min	S	117±10	77±5	83±9	0.160±0.02
	NG	96±9	69±4	96±7	0.121±0.01
	%	17.9	10.3	15.6	24.3
	P	<0.05	NS	<0.05	<0.01

SBP: Systemic blood pressure
DBP: Diastolic blood pressure

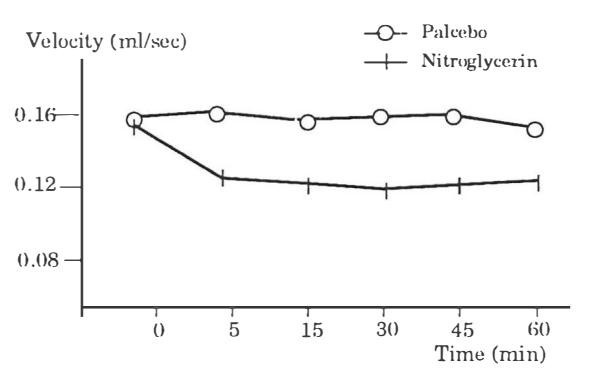
blood flow, systolic and diastolic blood pressures, and heart rate were monitored continuously 15,30,45 and 60 min after nitroglycerin or saline administration.

Statistical Analysis

The results are expressed as means ± SD. Two-way analysis of variance with replications and Student's t test for paired data were used for statistical comparison. Results were considered significant at $p<0.05$.

RESULTS

The values obtained before and after the administration of nitroglycerin and saline are listed in Table 2.



x: p< 0.001 significan different from basal value

Graphic 1: The values of portal blood velocity before and after the administration of nitroglycerin and saline.

Intravenous administration of nitroglycerin markedly reduced the portal blood velocity, systolic and diastolic blood pressure increased heart rate when the compare to saline infusion group. In the nitroglycerin group portal blood velocity fell by 22-29 % ($p<0.01$) systolic and diastolic blood pressure by 16-18% and 9-12.5 % ($p<0.05$), the heart rate increased by 15-18 % (Graphic 1), shows the changes in portal blood flow with time in the two groups of patients. No side effect were experienced by the patients who received nitroglycerin.

DISCUSSION

This study clearly has demonstrated that an intravenous infusion of nitroglycerin results in a significant reduction in portal blood flow in patients with cirrhosis of the liver. The some reports with nitroglycerin in cirrhosis has previously been published (13). But little work have been demonstrated by the pulsed Doppler system, is less invasive test (12).

In studies in humans, the administration of nitroglycerin has recently been shown to decrease intravascular esophageal variceal pressure in every patient receiving the drug (14); similarly isosorbide dinitrate has been shown to significantly decrease the hepatic venous pressure gradient (HVPG) in cirrhotic patients, a decrease that correlates well with a reduction in cardiac output (15).

Experimental data seem to suggest that there are two mechanisms through which nitrates reduce portal pressure (9,16,17). When nitroglycerin is administered in combination with vasopressin, it produces vasodilation of the portal-hepatic bed without diminishing the vasoconstrictive effect of vasopressin on the splanchnic arteries. Portal venous resistance is thereby reduced (16). Similarly, when nitrates are administered in high doses to portal-vein-constricted rats with a hyperdynamic circulation, the reduction in portal pressure is not accompanied by a decrease in portal blood flow, suggesting vasodilation of the portal-collateral system, which would be the result of a direct effect of nitrates on these vessels (17). On the other hand, when nitrates are administered in low doses, alone or in combination with propranolol, a significant increase in splanchnic arterial resistance and a decrease in portal blood flow was observed along with a reduction in portal pressure, an effect that is likely the result of splanchnic arterial vasoconstriction, mediated by low pressure baroreflexes and stimulated by both a mild reduction in arterial pressure and the venous pooling effect of nitroglycerin (9). In this case, the reduction in portal pressure is mediated by a decrease in portal blood flow.

Nitroglycerin decreases portal pressure either by decreasing the portal venous inflow (9) or by decreasing the resistance to the blood flowing in the portal system or both (13,16).

Nitroglycerin that reduce portal pressure could theoretically be useful in the prevention and/or treatment of variceal hemorrhage. Furthermore, the observation that nitroglycerin administration reduces variceal pressure in all patients that received the agent (14) seems to indicate that either by reducing gastroesophageal collateral blood flow or by dilating the portal-hepatic bed, nitroglycerin decreases intravariceal pressure and, therefore, one of the main determinants of variceal rupture (18). Of the 11 patients studied, two did not show a reduction in HVPG in spite of reductions in blood pressure. Failure to respond to nitrates have been observed during the administration of isosorbide dinitrate (19,20).

Although we have shown that nitroglycerin reduces HVPG, the fact that this reduction is accompanied by a significant reduction is accompanied by a significant reduction in arterial blood pressure, might limit its use in clinical parctice which produced symptoms related to hypotension (13). However, studies in experimental animals have shown that reductions in portal pressure can be achieved with doses that reduce blood pressure only minimally (9). Therefore, the use of nitroglycerin in the treatment of portal hypertension should be explored.

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