Influence of portal pressure change on intestinal permeability in patients with portal hypertension

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Objective: **To investigate intestinal permeability in patients with portal hypertension and its relationship with portal pressure.**

Methods: **Twenty patients with portal hypertension were divided into two groups (A, B), 10 patients per group. In group A, patients were treated with combined transjugular intrahepatic portosystemic shunt (TIPS) and modified Sugiura. In group B, patients were treated with modified Sugiura only. Intestinal permeability was assessed before operation, two weeks after TIPS, and two weeks after modified Sugiura; 20 healthy control subjects were also assessed.**

Results: **Intestinal permeability was significantly higher in the patients than in the control group ($P < 0.01$). In group A, portal pressure, intestinal permeability decreased two weeks after TIPS ($P < 0.05$), and no obvious change was noted two weeks after modified Sugiura; but they were significantly lower than those before TIPS ($P < 0.05$). In group B, intestinal permeability was not different before and after operation. Intestinal permeability in group A was not different from that in group B before treatment, but significantly lower after modified Sugiura ($P < 0.05$). Portal pressure was significantly correlated with intestinal permeability ($r = 0.627$, $P < 0.01$).**

Conclusions: **This study shows that combined TIPS and modified Sugiura can lower portal pressure and intestinal permeability, and enhance the therapeutic efficacy on portal hypertension.**

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Key words: **portal hypertension; portasystemic shunt; surgery; intestinal permeability**

Introduction

At present, studies of intestinal permeability are rare or confined in pre-treatment stage for patients with portal hypertension. The relationship between intestinal permeability and portal pressure has not yet been studied, let alone their changes after treatment.

In the treatment of portal hypertension, the principal goals are to decrease portal pressure, maintain hepatic function, and control esophageal varices bleeding. In this sense, the combined treatment of transjugular intrahepatic portosystemic shunt (TIPS) and modified Sugiura can be considered suitable under these conditions.[1] In this study, we assessed the change in and relationship between portal pressure and intestinal permeability before and after treatment.

Methods

Patients

Twenty patients with portal hypertension due to cirrhosis were enrolled in the study (mean age 47.8 ± 11.3 years, 14 men and 6 women). Liver cirrhosis was proved by biopsy in all patients. The severity of liver cirrhosis was assessed according to Child-Pugh classification. The causes of cirrhosis were virus, alcoholism and schistosome. All the patients suffered from esophageal varices, splenomegaly and hypersplenia. The 20 patients were divided into two groups, 10 per group. In group A (Child A in 2 patients, Child B in 4, Child C in

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4), the patients were treated with combined TIPS and modified Sugiura. All of them had esophageal bleeding, and 8 had severe ascites. In group B (Child A in 3 patients, Child B in 7), the patients were treated with modified Sugiura only. Six of these patients had esophageal bleeding but ascites. Alcoholic beverage was banned for at least 4 weeks before admission into our Department. Twenty healthy volunteers (mean age 24.7±3.8 years, 11 men and 9 women) served as a control group.

Methods

In group A, portal pressure and intestinal permeability were measured before TIPS, two weeks after TIPS, and two weeks after modified Sugiura.

In group B, intestinal permeability was measured before the treatment and two weeks after modified Sugiura. In the group treated with modified Sugiura only, portal pressure was measured during the operation.

Intestinal permeability was assessed in all healthy volunteers. Informed consent was obtained from all the participants before the study.

Procedures

Portal pressure

In group A, portal pressure was directly measured through a catheter detained in the portal vein. In group B, portal pressure was measured during the operation.

Intestinal permeability

Lactulose (LAC) in the usual treatment of patients was not given 3 days before a lactulose/mannitol test was performed. Intestinal permeability was assessed using the test in patients with stable conditions. None of them had a urinary tract infection during the test. The test was also performed in the healthy volunteers.

After 10-hour fasting, each subject ingested 50 ml water containing 10 g LAC and 5 g MAN. Before ingestion of test sugar, each subject was asked to empty her/his bladder completely. Thereafter, urine was collected during 6 hours. Urine volume was recorded and aliquots of urine were stored at -20 ℃ for subsequent analysis. The concentrations of LAC and MAN in the urine were quantitated by high performance liquid chromatography (HPLC). The urinary excretion rates of LAC (LAC%) and MAN (MAN%) were measured and the LAC/MAN ratio was calculated.

Statistical analysis

All data were expressed as $\bar{x} \pm s$. t test was used for statistical analysis, and linear regression for correlation analysis. P value <0.05 was considered statistically significant.

Results

All patients in group A were successfully treated with combined TIPS and modified Sugiura. After TIPS, esophageal varices bleeding was well controlled, ascites was eliminated, and the patients had no operative complications. After being modified, direct portal vein angiography showed absence of the coronary vein, and upper digestive tract barium meal showed relief or elimination of esophageal varices. After combined treatment, bleeding of the abdominal cavity occurred in one patient, and subsequent surgical hemostasis was performed. Two patients who had experienced hepatic encephalopathy during the operation were cured by medication. In group B, after modified Sugiura, 2 patients showed intractable ascites, 3 presented with infection, and 1 died of deseminated intravenous coagulation secondary to infection.

The parameters between the patients and controls showed no significant difference in mannitol excretion but obvious increase in lactulose excretion ($P<0.01$) (Table 1). The intestinal

Table 1. Comparison between patients and control subjects

	Patients ($n=20$)	Control($n=20$)	$P<$
LAC (%)	1.562±0.349	0.348±0.043	0.01
MAN (%)	13.97±0.86	15.82±0.61	NS
Intestinal permeability	0.132±0.110	0.032±0.018	0.01

Table 2. Comparison between groups A and B ($n = 10$)

	Group A			Group B	
	Pre-TIPS	2 weeks post-TIPS	2 weeks after Sugiura	Pre-operation	2 weeks after Sugiura
Intestinal permeability	0.128 ± 0.072	0.050 ± 0.029 *	0.036 ± 0.015 *Δ	0.135 ± 0.143@	0.115 ± 0.086&☆
Portal pressure (cmH_2O)	40.9 ± 2.7	31.8 ± 1.5#	30.5 ± 1.3#Δ	39.3 ± 2.2@	–

*: $P < 0.05$ before vs after treatment in group A. #: $P < 0.01$ before vs after treatment in group A. Δ: not significant (NS) 2 weeks after TIPS vs 2 weeks after Sugiura in group A. @: NS before treatment in group A vs B. &: NS before vs after treatment in group B. ☆: $P < 0.05$ 2 weeks after Sugiura group A vs B.

permeability (L/M ratio) was significantly different between the two groups.

Intestinal permeability and portal pressure decreased significantly 2 weeks after TIPS in group A and didn't change much after modified Sugiura, but they were lower than those before TIPS. In group B, intestinal permeability changed nothing before and after operation. Comparison showed that intestinal permeability was not different in groups A and B before operation, but the data from group A were lower than those in group B after modified Sugiura (Table 2).

To investigate the role of portal pressure before and after treatment in group A, we analyzed the correlation between portal pressure and intestinal permeability, and found that portal pressure is significantly correlated with intestinal permeability ($r = 0.627$, $P < 0.01$).

Discussion

Portal hypertension due to cirrhosis is one of severe complications of liver disease. Its clinical manifestations include esophageal varices, hepatic encephalopathy, ascites, spontaneous bacterial peritonitis (SBP) and endotoxemia, which threaten the life of patients or induce a high fatality rate. Therefore, the principles of treatment are to maintain hepatic function, lower portal pressure, and control esophageal varices bleeding. The combined treatment of TIPS and modified Sugiura is a new method which has been adopted at our hospital since 1996. After operation, esophageal varices bleeding stopped in addition to the disappearance of ascites and maintenance of hepatic function. Clinical results have shown that the combined treatment is effective for portal hypertension.

In this study, we observed the changes and relations of portal pressure and intestinal permeability before and after treatment.

In patients with portal hypertension, portal pressure consists of physiological portal pressure, obstructive portal pressure and functional portal pressure. The obstructive portal pressure results from hepatocyte damage leading to deformity and structural change of the liver. The functional portal pressure is due to malmetabolism, increased portal blood flow, or increased portal resistance. Then comes the question that why the combined treatment of TIPS and modified Sugiura could effectively decrease portal pressure. The answer lies not only in possibly lowered obstructive portal pressure, but also in lower functional portal pressure because of intrahepatic diffluence tract.

Intestinal permeability is assessed in vivo non-invasively by measuring urinary excretion of orally administered test substances such as ethylene glycol polymers, oligosaccharides, monosaccharides and non-degraded radiolabelled chelates. An impaired intestinal permeability is involved in a large variety of clinical conditions, including coeliac disease, intestinal infection, inflammatory bowel disease, and malignancy. Higher intestinal permeability may be hypothesized in liver cirrhosis, which may account for endotoxemia, bacterial translocation, and increased risk of bacteraemia, and SBP. Previous studies have failed to show abnormal intestinal permeability in liver cirrhosis, as proved normal urinary LAC/MAN excretion ratio. However, the number of patients was smaller than that in our study and patients with an advanced disease were not investigated. Recently, in-

creased intestinal permeability has been found in patients with cirrhosis.[2-6] In our study, intestinal permeability was significantly higher in 20 patients with portal hypertension due to cirrhosis than in controls.

The main mechanism of increased intestinal permeability may be portal hypertension due to esophageal varices. In portal hypertension, intestinal mucosal blood flows in a slower velocity, and submucous capillaries and veins are in phlebectasia and congestion. The transportation time of oxygen and nutrients to mucosa is elongated, and so metabolite can not move out in time. The microcirculation of intestinal mucosa is disturbed, and the mucosa of the bowel wall is ischemic. Literatures[7] showed that in portal hypertension venulae and capillary telangiectasia reaches 70%, and that total blood flow is increased but effective blood flow of the intestinal mucous membrane is not enough. The change of blood flow will lead to hyperemia, edema and erosion in the intestinal mucosa. Mucosal epithelial cells and submucous capillaries show pathological changes, which weaken the function of intestinal barrier and increase intestinal permeability. Moreover, impaired hepatic function in cirrhotic patients will lead to malmetabolism of hormones. Literatures showed that glucagon is increased 2-6 folds over the normal value. Glucagon will selectively dilate the precapillary sphincter contributing to increased portal pressure. Moreover, glucagon accelerates local metabolism, thus oxygen consumption is increased and mucosal lesion aggravated. Impaired hepatic function will reduce the resistance to virulence factor, and poor albumin production will weaken the capacity of mucosal plerosis. Endotoxin activates a lot of cytokines at the same time, resulting in tissue ischemia and hypoxia and further in malmetabolism and increased intestinal permeability.[5,7]

Campillo et al[2] found that lactulose excretion hardly changes in cirrhotic patients while mannitol excretion is sharply reduced, leading to a higher LAC/MAN ratio. They suggested that mannitol absorption occurs across the intestinal villi by both transcellular and paracellular pathways and hence is most influenced by changes in the total surface area of the small intestine. In contrast, lactulose absorption primarily occurs across the larger pores located at the tight junctions between crypt cells. The permeation by this latter route is influenced mostly by pathological processes that affect the integrity of intestinal tight junction rather than by disease processes that affect the area of absorptive surface. Therefore, their results suggest that a defect in intestinal surface area is the main cause for abnormalities of urinary probes excretion in cirrhotic patients. In this study, however, mannitol excretion in patients tended to be lower than in controls, but the difference was not significant. In contrast, lactulose excretion in patients was elevated markedly and significantly. This may be caused by an alteration in the tight junctions secondary to edema. Studies have indicated that intercellular junctions are widened and mediated by intracellular messengers such as cAMP, activation of Na-couple nutrient transporters and the tensile force from an intracellular sphincter-like actinomycin ring.[8] Recently, Such et al[9] observed a distended interenterocyte space with intestinal epithelial cells closely attached by morphologically intact tight junctions in cirrhotic patients. Keshavarzian et al[5] also held that mannitol excretion mainly represents functional gut surface area rather than intestinal permeability. Hence, an increased L/M ratio does not necessarily imply an increase in intestinal permeability unless it is associated with an increase in lactulose excretion.

After combined operation, decreased portal pressure and ameliorated portal circulation improve the congestion of intestinal mucous membrane, increase effective mucosal flow, and alleviate ischemia and hypoxia. In addition, decreased portal pressure may lower the levels of NO and endotoxin, thus improving portal high-dynamic circulation and relieving the vicious cycle caused by endotoxin-activated cytokines.[7] Finally effective liver flow is maintained to have normal hepatic function after hepatic arterial infusion.

In our study, a significant correlation was observed between intestinal permeability and portal pressure in group A before and after operation, showing that the change of portal pressure is the

direct cause of intestinal permeability change. In contrast, the decreased portal pressure, ameliorated congestion of the mucosa, and improved intestinal permeability further proved the correlation. The treatment with modified Sugiura, however, was not effective in lowering either portal pressure or intestinal permeability, indicating that portal pressure plays an important role in the change of intestinal permeability. In group B, the patients were treated with modified Sugiura only, neither portal pressure decreased nor intestinal permeability improved, with a high morbidity of bacterial translocation. In fact, infection was the first complication in patients of group B. But the incidence of infection in patients of group A was low, because portal pressure was decreased to improve intestinal permeability after combined treatment.

The principle for the treatment of portal hypertension due to cirrhosis is not only the maintenance of hepatic function, but also decrease of portal pressure and blocking of the lateral branch. Clinical investigation shows that the combined treatment of TIPS and modified Sugiura can not only decrease portal pressure and control esophageal varices bleeding, but also prevent bleeding and maintain hepatic function.

In conclusion, intestinal permeability is increased in patients with portal hypertension. The combined TIPS and modified Sugiura as a new method for the treatment of portal hypertension can decrease portal pressure and improve portal circulation, thus lowering intestinal permeability. But the treatment with modified Sugiura only could not change intestinal permeability. Hence the combined treatment can relieve infections due to bacterial translocation, especially endotoxemia.

Competing interest

No benefits in any form have been received or will be received from a commercial party related directly or indirectly to the subject of this article.

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