

# Dextranum in Combination with Low-Molecular-Weight Heparin Prevents the Portal Vein Thrombosis after Splenectomy for Portal Hypertension

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## Dong *et al.*: Dextranum in Combination with Low-Molecular-Weight Heparin Prevents the Portal Vein Thrombosis

This study aimed to explore the effect of dextranum in combination with low-molecular-weight heparin on the prevention of portal vein thrombosis after splenectomy for portal hypertension. Between February 2015 and February 2019, we enrolled 128 liver cirrhosis patients with portal hypertension as the subjects which were later divided randomly into the observation group and the control group, with 64 patients in each group. All patients received the splenectomy in combination with the esophagogastric devascularization. Following the surgery, dextranum was given to the patients in two groups for prevention of portal vein thrombosis, while those in the observation would additionally took low-molecular-weight heparin for prophylaxis of portal vein thrombosis. After medication, incidence of portal vein thrombosis after surgery was recorded, and at 1 d and 14 d after surgery, the platelet count in peripheral blood was also detected; furthermore, we recorded the condition of patients in preventive anti-coagulation treatment, oral administration of enteric-coated aspirin, postoperative hospitalization days and the incidence of complications, including gastrointestinal bleeding and liver failure, within 3 mo after operation. In the observation group, the incidence rate of postoperative portal vein thrombosis was 9.37 %, significantly lower than 31.25 % in the control group ( $p < 0.05$ ), while the difference in the platelet count test at 1 d after operation showed no statistical significance ( $p > 0.05$ ), and the platelet count test showed an increasing trend at 14 d after operation ( $p < 0.05$ ); however, the intergroup comparison showed no significant difference ( $p > 0.05$ ). Between two groups, the duration of preventive anti-coagulation treatment and oral administration of aspirin showed no significant difference ( $p > 0.05$ ), while the patients had a shorter hospitalization duration in the observation group than their counterparts in the control group ( $p < 0.05$ ). Within 3 mo after operation, the incidence rate of complications, including gastrointestinal bleeding and liver failure, in the observation group was 6.25 %, significantly lower than 26.56 % in the control group ( $p < 0.05$ ). After splenectomy for portal hypertension, dextranum in combination with the low-molecular-weight heparin can prevent the portal vein thrombosis by inhibiting the platelet aggregation, thereby promoting the patients' recovery and decreasing the incidence of postoperative complications.

**Key words:** Heparin, low molecular weight, venous thrombosis, splenectomy, gastrointestinal hemorrhage, liver cirrhosis

Liver cirrhosis is a common, chronic, progressive liver disease in clinical practice, and in early stage, patients show no evident clinical manifestations, while as the disease progresses, liver cirrhosis is manifested by the portal hypertension (PHT)<sup>[1]</sup>. PHT, as the common clinical manifestation of liver cirrhosis in advanced

stage, may induce the hepatic encephalopathy, or even death<sup>[2]</sup>. As a major method for treatment of PHT, splenectomy makes patients more susceptible to the postoperative portal vein thrombosis (PVT), with a high incidence rate of nearly 30 %<sup>[3]</sup>. PVT is a rare deep, venous, occlusive disease, refers to the thrombus

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that emerges in the spleen veins, superior mesenteric veins and main portal vein, with clinical manifestations of fever, abdominal pains, dilation or diarrhea and in some particular cases, threatening the life of patients<sup>[3]</sup>. Clinically, the major strategy to prevent PVT includes the medication and functional exercise in an early stage, while the latter strategy can only alleviate the symptoms, but fail in prevention<sup>[4]</sup>. In early medication, dextranum is preferred for its ability to dilute the blood, and reduce the platelet adhesion and aggregation<sup>[5]</sup>. In recent y, accumulating evidence suggests that low-molecular-weight heparin, as the common anti-coagulation drug, is efficient in prophylaxis of thrombus by inhibiting the involvement of xabans (Xa inhibitors) in thrombosis, with the significant anti-thrombus effect<sup>[6]</sup>. In this study, we explored the effect of dextranum in combination with the low-molecular-weight heparin on the PVT after splenectomy for PHT, so as to prevent the prognosis of patients. Detailed information is reported as follow. In this retrospectively analysis, we enrolled 128 liver cirrhosis patients with PHT who were admitted to this hospital between February 2015 and February 2019 for treatment. Inclusion criteria: Patients with the pathological diagnosis of liver cirrhosis with PHT; patients with intact clinical data; patients who volunteered to sign the written informed consents; patients with no PVT before operation. Exclusion criteria: Patients in pregnancy or lactation; patients with the organic damage, showing the obvious tendency of bleeding; patients with the history of heparin-led thrombocytopenia. Randomly, patients were divided into the observation group and the control group, with 64 patients in each group. Comparison of the general data of patients between two groups showed no significant differences ( $p>0.05$ ; Table 1), suggesting that the general data of these two groups were comparable. The protocol of this study was approved by the Ethical Committee of the hospital. For all patients, they underwent the splenectomy in combination with the esophagogastric devascularization. Control group: Patients took 500 mL dextranum via intravenous infusion at 1 d after operation, once per d for 7 d. Observation group: In addition to dextranum, patients took 3800 IU (0.4 mL) low-molecular-weight heparin via subcutaneous injection at 1 d after operation, once per d. Following ten d of treatment, patients took the warfarin (2.5 mg) and aspirin (5.0 mg) via oral administration. Recording the incidence of postoperative PVT according to the ultrasonic criteria of 50 % to 100

% of blockage in portal veins to determine the extension of superior mesenteric vein; Recording the peripheral Platelet Count Test (PLT) count at 1 d and 14 d after operation; Recording the duration of preventive anti-coagulation treatment and oral administration of aspirin and the postoperative hospitalization d; Recording the incidence of complications, including gastrointestinal bleeding and liver failure, within 3 mo after operation. SPSS 20.0 software was used to analyze the data of this study. Measurement data in normal distribution were presented in form of mean $\pm$ standard deviation (SD) and compared between two groups by using the t test. Enumeration data were presented by the number of cases, and compared by using the chi-square test.  $\alpha=0.05$  was set as the inspection level and  $p<0.05$  suggested that the difference had statistical significance. In the observation group, the incidence rate of postoperative PVT was 9.37 %, significantly lower than 31.25 % in the control group ( $p<0.05$ ; Table 2). The difference in the PLT at 1 d after operation showed no statistical significance ( $p>0.05$ ), and the PLT showed an increasing trend at 14 d after operation ( $p<0.05$ ); however, the intergroup comparison showed no significant difference ( $p>0.05$ ; Table 3). Between two groups, the duration of preventive anti-coagulation treatment and oral administration of aspirin showed no significant difference ( $p>0.05$ ), while the patients had a shorter hospitalization duration in the observation group than their counterparts in the control group ( $p<0.05$ ; Table 4). Within 3 mo after operation, the incidence rate of complications, including gastrointestinal bleeding and liver failure, in the observation group was 6.25 %, significantly lower than 26.56 % in the control group ( $p<0.05$ ; Table 5). Liver cirrhosis usually complicates the incidence of PHT, while PVT is the common, severe complication of splenectomy for PHT, usually manifested by the acute thrombus, or even death in some severe cases<sup>[7]</sup>. Current research shows that factors contributing to PVT include the hypercoagulability, increase in PLT, anomaly in function, decrease in erythrocyte deformability, slowness in blood flow of the portal vein system and aggravation in blood stagnation<sup>[8]</sup>. In this study, in the observation group, the incidence rate of postoperative PVT was 9.37 %, significantly lower than 31.25 % in the control group, while the duration of preventive anti-coagulation treatment and oral administration of aspirin showed no significant difference, and the patients had a shorter hospitalization duration in the observation

group than their counterparts in the control group, suggesting that the combined strategy can effectively prevent the incidence of postoperative PVT to facilitate the recovery of patients<sup>[9]</sup>. Low-molecular-weight heparin, the constituents or fragments derived from the degradation of heparin in 1/3 to 1/2 of the relative molecular weight of heparin, is excellent in bioavailability and long half-life in comparison with the heparin; nevertheless, low-molecular-weight heparin also possess the anti-coagulation activity of the regular heparins, but without their adverse reactions. Due to the hidden onset and lack of specific manifestations of PVT, any delay in treatment can cause destructive outcomes. Plus, splenectomy can further aggravate PHT, possibly inducing the prehepatic congestion and deteriorating the liver dysfunction, thereby promoting the progression of PHT<sup>[10]</sup>. In this study, we found that in the observation group, the incidence rate of postoperative PVT was 9.37 %, significantly lower than 31.25 % in the control group, while the difference in the PLT at 1 d after operation showed no statistical significance, and the PLT showed an increasing trend at 14 d after operation; however, the intergroup comparison showed no significant difference. This may attribute to the fact that the combined strategy can inhibit the PLT cyclooxygenase to enhance the acetylation of serine in the active center to decrease the aggregation of PLT. Within 3 mo after operation, the incidence rate of complications, including gastrointestinal bleeding and liver failure, in the observation group was 6.25 %, significantly lower than 26.56 % in the control group ( $p < 0.05$ ). PVT is inevitable for patients after any surgery methods for PHT<sup>[11]</sup>. PVT can further deteriorate the liver dysfunction, decrease the synthesis and storage of plasma albumin, and induce

the refractory ascites<sup>[12]</sup>; besides, thrombus can spread to the superior mesenteric vein to cause the congestion and dysfunction in mesenteric vessel to induce the intestinal ischemia; in the inferior layer of gastric mucosa, the abnormal blood flow, and the newly developed variceal vessels surrounding the fundus and cardia of stomach that triggers the recurrence of varix after devascularization, and the gastrointestinal bleeding<sup>[13]</sup>. In this study, within 3 mo after operation, the incidence rate of complications, including gastrointestinal bleeding and liver failure, in the observation group was 6.25 %, significantly lower than 26.56 % in the control group, which is because the dextranum can dilute the blood to reduce the adhesion and aggregation of PLT, while low-molecular-weight heparin can promote the lysis of fibrous protein to prevent the thrombosis. Meanwhile, in the preventive measures, spleen veins should be shortened and the intraoperative blood infusion should be minimized<sup>[14]</sup>. Moreover, bleeding risk should be aware in administration of low-molecular-weight heparin, and the dosage should be individualized upon the patient's condition, which should be further noted in combined medication<sup>[15]</sup>. In this study, there remain some shortages, including the insufficient sample size, the lack of representativeness of the subjects and the inadequacy in research into the mechanism, which will be resolved in later studies. To be concluded, after splenectomy for portal hypertension, dextranum in combination with the low-molecular-weight heparin can prevent the PVT by inhibiting the platelet aggregation, thereby promoting the patients' recovery and decreasing the incidence of postoperative complications.

**TABLE 1: COMPARISON OF THE GENERAL DATA OF PATIENTS BETWEEN TWO GROUPS**

Group	n	Liver function (A/B/C)	Width of portal vein (cm)	Primary disease (hepatitis/ alcoholic liver disease)	Gender (Male/ female)	Age (y)	BMI (kg/m <sup>2</sup> )
Control group	64	22/31/11	1.53±0.46	33/31	41/23	56.21±4.58	22.84±2.75
Observation group	64	21/30/13	1.49±0.53	35/29	38/26	56.10±5.12	22.12±3.03
t		0.045	0.078	0.221	0.392	0.114	0.274
p		>0.05	>0.05	>0.05	>0.05	>0.05	>0.05

mean±standard deviation

**TABLE 2: COMPARISON OF THE INCIDENCE OF POSTOPERATIVE PVT OF PATIENTS BETWEEN TWO GROUPS**

Group	n	PVT	Incidence rate of PVT (%)
Observation group	64	6	9.37
Control group	64	20	31.25
x <sup>2</sup>			4.991
p			<0.05

p<0.05 indicated the statistical significance of the difference.

**TABLE 3: COMPARISON OF THE DYNAMIC CHANGES OF PLT IN PERIPHERAL BLOOD BETWEEN TWO GROUPS**

Group	n	Postoperative 1 d	Postoperative 14 d	t	p
Observation group	64	86.34±18.34	570.31±56.34	15.296	<0.05
Control group	64	87.21±17.35	571.04±76.12	15.113	<0.05
t		0.123	0.079		
p		>0.05	>0.05		

Each data=Mean±SD×09/l. p<0.05 indicated the statistical significance of the difference.

**TABLE 4: COMPARISON OF THE RECOVERY TIME OF PATIENTS BETWEEN TWO GROUPS**

Group	n	Duration of preventive anti-coagulation therapy	Duration of oral administration of aspirin	Postoperative hospitalization days
Observation group	64	96.43±7.29	30.43±4.14	18.32±4.23
Control group	64	98.10±6.38	29.58±2.58	30.19±6.10
t		0.331	0.22	6.332
p		>0.05	>0.05	<0.05

mean±standard deviation.

**TABLE 5: COMPARISON OF THE INCIDENCE OF MAJOR COMPLICATIONS AFTER OPERATION BETWEEN TWO GROUPS**

Group	n	Gastrointestinal bleeding	Liver failure	Total
Control group	64	10	7	17(26.56)
Observation group	64	2	2	4(6.25)
x <sup>2</sup>				5.779
p				<0.05

p<0.05 indicated the statistical significance of the difference.

#### Author's contributions:

Chen Dong and Yulai You contributed equally to this work.

#### Conflict of interests:

The authors declared no conflicts of interest.

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