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Research article

Preventive use of low molecular weight heparin in portal vein system thrombosis after splenectomy without portal hypertension

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ABSTRACT

Background/aim: Portal vein system thrombosis (PVST) is a serious complication after splenectomy, and many researches focus on how to prevent PVST these years. The current study aimed to explore an effectively method to prevent PVST occur after splenectomy.

Methods: Records of patients performed with splenectomy from January 2018 to December 2020 were reviewed. Clinical parameters, including patient history, physical examination, and the results of laboratory investigations, were analyzed.

Results: One hundred and eighty patients (127 females) were included. Twenty-four patients were confirmed PVST by Color Doppler ultrasonography and CTA (thrombus group) and the others were not (non-thrombus group). One hundred and twenty patients were performed with laparoscopic splenectomy (LS) and 53 were open splenectomy (OS). Seventeen PVST were found in LS patients and 7 PVST were found in OS patients ($P = 0.974$). The average time of thrombosis was 4.48 ± 2.9 days after operation. The proportion of postoperative preventive use of low molecular weight heparin (LMWH) in non-thrombus group was higher than that in thrombus group (27.6% vs. 8.3%, $P = 0.045$). Compared with the non-thrombus group, the thrombus group showed significantly higher serum alanine transaminase (ALT) and aspartate transaminase (AST) 7 days after splenectomy (79.67 ± 39.1 U/L vs. 29.34 ± 2.5 U/L, $P = 0.001$; 192.4 ± 145.8 U/L vs. 30.54 ± 3.0 U/L, $P < 0.001$).

Conclusion: Laparoscopic splenectomy does not seem to increase the occurrence of PVST in patients without portal hypertension. Early postoperative preventive use of LMWH after splenectomy may prevent the formation of PVST.

1. Introduction

Splenectomy is a common surgical treatment for hypersplenism, splenic trauma and splenic tumor. Owing to the large population of hypersplenism patients caused by hepatitis cirrhosis and immunologic thrombocytopenic purpura (ITP), splenectomy is widely used in China. In recent years, due to less trauma and a faster postoperative recovery, laparoscopic splenectomy (LS) has become more and more popular in elective splenic surgery [1]. Portal vein system thrombosis (PVST), including portal vein thrombosis (PVT) and superior mesenteric vein thrombosis (SMVT), is a potentially life-threatening complication after splenectomy, and it has a concealed onset without any specific symptoms and signs [2, 3, 4]. The incidence of PVST has been reported significantly higher after LS than that of conventional open splenectomy (OS), but this conclusion is still controversial [5, 6, 7].

To date, many reports have noted that maybe liver cirrhosis and portal hypertension are closely related to thrombosis after splenectomy, which can be explained by the widening of the portal vein system

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diameter caused by cirrhosis, and the rapid increase of platelets level after splenectomy. However, there are few researches for splenectomy and PVST in patients without portal hypertension.

As for the prevention of PVST after splenectomy, in recent years, low-molecular weight heparin (LMWH), an anticoagulation drug, has been applied as a preventive measure after splenectomy. At the same time, the preventive role and the safety of LMWH have been under dispute [8, 9]. Studies have shown that LMWH may increase the risk of bleeding in patients with splenectomy, especially in patients with cirrhosis and coagulation disorders [10].

Therefore, we designed this retrospective study to confirm whether laparoscopic splenectomy increases the incidence of portal vein thrombosis in patients without portal hypertension, and to clarify the value of prophylactic LMWH treatment in reducing PVST after splenectomy.

2. Results

2.1. Overview

One hundred and eighty patients were included in the study. There were no hemorrhagic event in all the enrolled patients. Patients included 53 (29.4%) males and 127 (70.6%) females. The mean age of patients was 50 ± 15.7 (range, 16–90) years. Forty nine (27.2%) patients have hepatitis B surface antigen positive, but no cirrhosis and portal hypertension. A total of 24 (13.3%) patients were confirmed PVST by Color Doppler ultrasonography and CTA and the others were not. The average time of thrombosis was 4.48 ± 2.9 days after operation. According to whether patients suffered from PVST, all of the enrolled patients were divided into thrombus group (n = 24) and non-thrombus group (n = 156). There was no significant difference of preoperative liver and kidney function between patients with and without thrombus.

In the thrombus group, two patients received AngioJet aspiration thrombectomy combined with transcatheter thrombolysis, another 2 patients received AngioJet aspiration thrombectomy combined with transcatheter thrombolysis and anticoagulant therapy, and the other 20 patients had completed anticoagulation successfully.

One hundred and twenty patients were performed with laparoscopic splenectomy (LS) and 53 were open splenectomy (OS). Seventeen PVST were found in LS patients and 7 PVST were found in OS patients (P = 0.974).

2.2. Clinical factors related to PVST

All the patients' characteristics were shown in Table 1. The characteristics of patients with PVST were shown in Table 2.

Compared with the non-thrombus group, the thrombus group showed significantly higher serum alanine transaminase (ALT) (Figure 1A) and aspartate transaminase (AST) (Figure 1B) 7 days after splenectomy (79.67 ± 39.1 U/L vs. 29.34 ± 2.5 U/L, P = 0.001; 192.4 ± 145.8 U/L vs. 30.54 ± 3.0 U/L, P < 0.001).

In thrombosis group, 17 patients underwent LS and 7 underwent conventional OS. While in non-thrombotic group, 110 patients underwent LS and 46 underwent OS. There was no significant difference in the proportion of LS between the two groups (70.8% v.s. 70.5%, P = 0.974). There were no differences of perioperative serum platelet levels and serum D-dimer level between thrombus group and non-thrombus group (Figures 2 and 3).

The characteristics of patients with and without postoperative preventive use of low molecular weight heparin (LMWH) were shown in Table 1. The proportion of postoperative preventive use of LMWH in non-thrombus group was higher than that in thrombus group (27.6% vs 8.3%, P = 0.045). In patients who use LMWH, the incidence of PVST was significantly lower (4.4% vs 16.3%, P = 0.045).

3. Discussion

PVST can lead to venous pressure increase and intestinal wall congestion, which can cause gastrointestinal bleeding, intractable ascites, jaundice, hepatic encephalopathy, intestinal edema, acute ischemic necrosis, intestinal obstruction, and even endanger the lives of patients [11, 12]. The prognosis of portal vein thrombosis depends on the location of the thrombus, the impact on the pressure of the portal system, the degree of liver damage and intestinal congestion, and whether the diagnosis and treatment are timely. In our research, we found that the liver enzyme of PVST patients was significantly higher than that of patients without thrombosis within one week after splenectomy. This may be related to the changes in blood supply of the liver portal vein caused by thrombus in some patients, which may lead to necrosis of liver cells. In our clinical experience, we have also found many times that acute portal vein thrombosis often leads to the elevation of liver enzymes because it blocks the portal vein blood flow. This inference is based on anatomy. Of course, further mechanism needs more basic research.

Table 1. Patients' Characteristics for PVST and LMWH cohorts.

	Thrombus group (n = 24)	Non-thrombus group (n = 156)	*P*	LMWH group (n = 45)	Non- LMWH group (n = 135)	*P*
Age	51 ± 15.4	50 ± 15.8	0.702	48 ± 14.3	50 ± 16.2	0.481
Gender (male/female)	10/14	73/83	0.667	20/25	63/72	0.864
Hospitalized duration (day)	17 ± 1.5	16 ± 0.8	0.150	17 ± 1.8	17 ± 0.7	0.705
HBsAg (+/-)	7/17	42/114	0.809	11/34	38/97	0.702
DM (+/-)	2/22	10/146	0.664	1/44	11/124	0.299
Hypertension (±)	3/21	27/129	0.770	8/37	22/113	0.820
Tobacco smoke (±)	2/22	27/129	0.377	7/38	22/113	1.000
Operation Time (min)	145.6 ± 8.9	149.7 ± 3.7	0.782	148.3 ± 8.4	149.4 ± 3.7	0.887
LS (%)	17 (70.8)	110 (70.5)	0.974	35 (77.8)	92 (68.1)	0.260
Preventive use of LMWH (%)	2 (8.3)	43 (27.6)	0.045	/	/	/
PVST (±)	/	/	/	2/43	22/113	
Pathologic Types (etiology)			0.341			0.156
Tumor-like lesions	1	13		3	11	
Vasculogenic tumor	14	77		16	75	
NHL	5	16		5	16	
Traumatic rupture spleen	3	33		1	35	
ITP	1	17		2	16	

DM: Diabetes Mellitus; LS: laparoscopic splenectomy; LMWH: low molecular weight heparin; NHL: non-Hodgkin's lymphoma; ITP: immunologic thrombocytopenic purpura.

Table 2. Patients characteristics with PVST.

	Operation						Thrombus Location					Treatment	
Patient No.	LS	OS	Gender	Hospitalization (days)	Age	Preventive use of LMWH	SMV	SV	PV trunk	PV branch	HV	Intervene	Medication
1		+	F	25	48	+				+			+
2	+		F	29	62			+					+
3	+		F	21	52					+			+
4		+	M	23	71			+					+
5	+		F	16	68				+				+
6	+		F	21	30					+			+
7	+		F	10	60			+	+	+			+
8	+		M	12	56					+			+
9		+	M	42	66			+		+			+
10		+	M	20	29			+					+
11	+		F	16	55			+	+	+		+	
12	+		F	11	62			+					+
13		+	M	15	41			+	+	+			+
14	+		M	17	64				+	+		+	
15	+		M	9	59					+			+
16	+		F	6	26					+			+
17	+		M	12	51			+		+			+
18	+		M	16	22					+			+
19		+	M	21	61			+	+				+
20	+		F	20	31		+	+					+
21	+		F	18	55			+	+	+		+	+
22		+	F	22	71		+		+				+
23	+		F	13	28			+	+	+	+	+	+
24	+		F	16	56	+	+	+	+	+			+

LMWH: low molecular weight heparin; LS: Laparoscopic splenectomy, OS: open splenectomy; SMV: Superior mesenteric vein; SV: Splenic vein; PV: portal vein; HV: hepatic vein; Gender: F means female, M means male; +: yes.

Some researchers have shown that the incidence of PVST in open splenectomy is about 1.6%–11%, which is much lower than that after laparoscopic splenectomy [13, 14, 15]. Many scholars believe that the incidence of thrombosis after LS is higher than that of OS. This may be attributed to the pneumoperitoneum established during LS that changes the hemodynamics of the splenic portal venous system, and leading to a high incidence of PVST [16, 17].

Also, the use of ultrasonic scalpel and linear cutting and closing device may cause tissue and vascular endothelial damage, thus leading to thrombosis [18].

Some other scholars also believe that the formation of thrombus is not particularly related to the operation itself. Although LS greatly shortens the length of hospitalization, due to early discharge and improper monitoring or prevention of thrombosis, the diagnosis of PVST after discharge from the hospital is often delayed.

There are also some researches show that LS is not significantly related to the occurrence of PVST [6, 7].

Our results show that there is no significant difference of PVST incidence between the OS and laparoscopic splenectomy. This results need to take into account the small sample size in this study. In the future, further multicenter studies with large patient samples are required to overcome the above-mentioned limitations and confirm our findings.

Whether preventive anticoagulation can effectively prevent PVST is still controversial [19, 20]. Aspirin, warfarin, LMWH and other anticoagulant drugs have been routinely used in patients after splenectomy. LMWH is the most frequently adopted preventive therapy in recent years, and it can suppress the activation of thrombin and formation of thrombosis by inhibiting the function of factor Xa. While, some studies believe that although LMWH can effectively prevent the occurrence of PVST, it also increases the risk of postoperative bleeding, especially in liver cirrhosis patients with coagulation disorders [9]. However, in Yang's meta-analysis, the patients who use LMWH prophylactically after splenectomy do not have an increased risk of bleeding [15]. When is the best time to use LMWH? It is generally believed that early use can more effectively prevent PVST [21]. In this study, we used 4200 IU of LMWH subcutaneously on the day after the operation, and then every 12 h a day from the next day.

In conclusion, LS does not seem to increase the occurrence of PVST in patients without portal hypertension. Early postoperative preventive use of LMWH after splenectomy may prevent the formation of PVST.

4. Patients and methods

4.1. Patients

The present study retrospectively analyzed the clinical data of a total of 180 patients who underwent splenectomy without liver cirrhosis between January 2018 and December 2020 at the Affiliated Hangzhou First People's Hospital and First Affiliated Hospital, Zhejiang University School of Medicine, China. Patients who had a preoperative history of portal vein thromboembolism, had received preoperative anticoagulation treatment, or with incomplete records missing some of the vital data required for the study were excluded.

Ethical approval of the study was obtained from the Ethics Committee of the Affiliated Hangzhou First People's Hospital and First Affiliated Hospital, Zhejiang University School of Medicine, the current regulation of the Chinese Government and the Declaration of Helsinki. Every precaution has been taken to protect the privacy of research subjects and the confidentiality of their personal information. Informed consent was obtained from all patients. The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

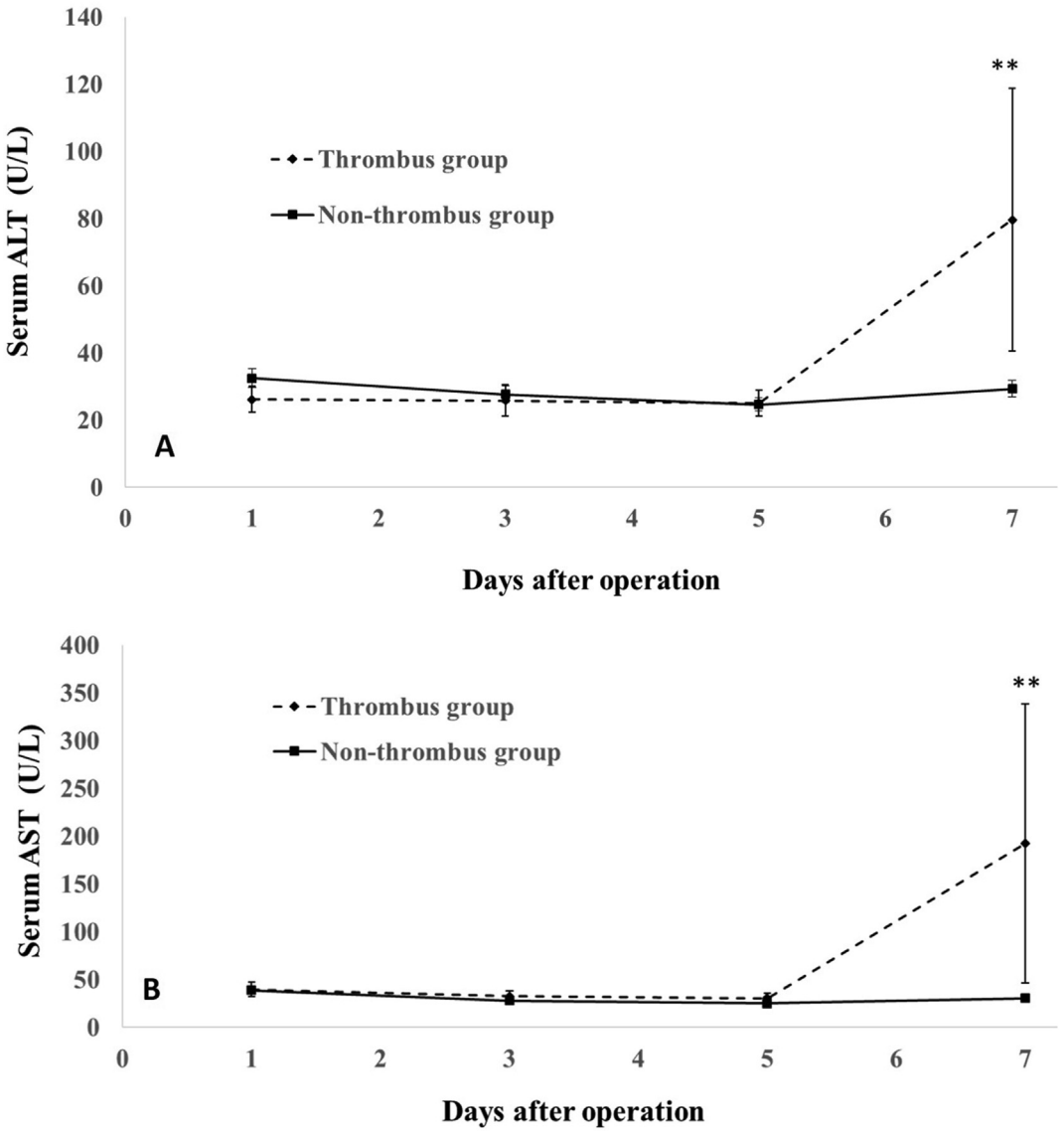

Figure 1. The comparison of liver function after splenectomy. Compared with the non-thrombus group, the thrombus group showed significantly higher serum alanine transaminase (ALT) (A) and serum aspartate transaminase (AST) (B) 7 days after splenectomy (*$P < 0.05$, **$P < 0.01$).

4.2. Laboratory and imaging examination

Complete blood count (CBC), coagulation function, liver function and kidney function were monitored every day for the first 3 days after splenectomy, then every other day.

Color Doppler ultrasonography was routinely performed on the first, third and seventh days after splenectomy.

Every PVT was diagnosis firstly by ultrasound and confirmed by CTA. If the ultrasound indicates maybe portal vein system thrombosis occur, upper abdominal computed tomography angiography (CTA) will be performed to confirm the occurrence of thrombosis.

4.3. Treatment

4.3.1. Preventive anticoagulation therapy

4200 IU of low-molecular-weight heparin (LMWH) was injected subcutaneously every 12 h a day for 7 days after splenectomy for some patients (Fraxiparine is used most of the time). Then, aspirin (100 mg) or clopidogrel (75 mg) was administered orally once daily from the eighth day to the 30th day after splenectomy. The remaining patients do not use LMWH routinely but aspirin or clopidogrel was administered orally once daily.

4.3.2. Therapy for thrombosis

According to the location, degree of thrombosis and liver function, single or combined treatment of interventional therapy (AngioJet aspiration thrombectomy or transcatheter thrombolysis) and medication (aspirin or clopidogrel) regimens are given respectively. Generally speaking, after 1 day of anticoagulation, if the symptoms related to portal hypertension are not relieved, we will use single or combined treatment of interventional therapy above.

4.4. Statistical analysis

The statistical analysis was performed using the statistical software IBM SPSS software (Ver. 19.0; SPSS Inc, Chicago, IL, USA). Quantitative variables are expressed as the mean ± standard deviation or median and range depending on the distribution. Categorical variables are presented as values and percentages. Student's t-test was used to compare quantitative variables. The chi-square test was used to compare categorical

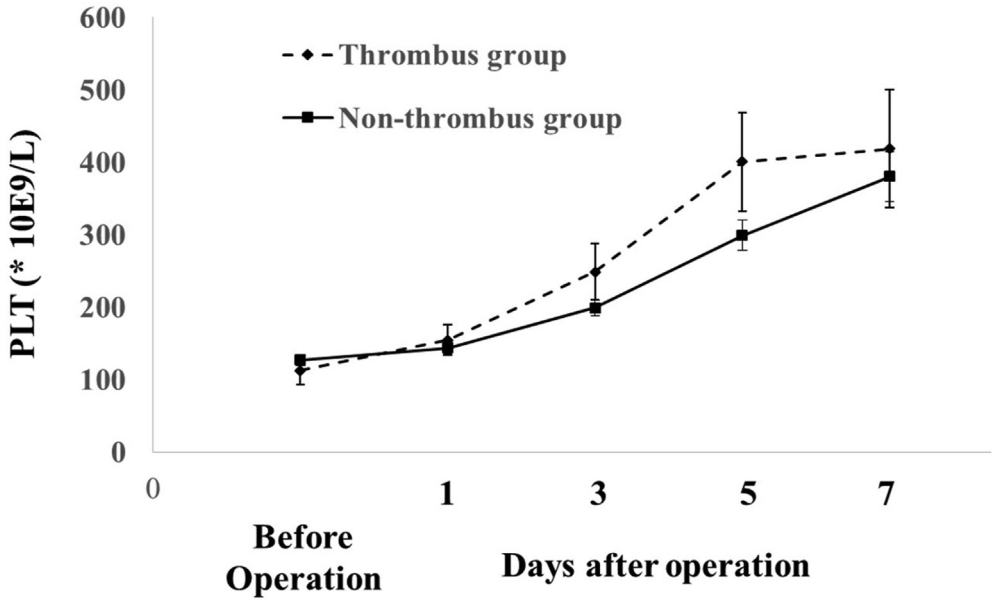

Figure 2. The serum platelet levels (*10E9/L) following splenectomy did not differ significantly between the 2 groups ($P > 0.05$).

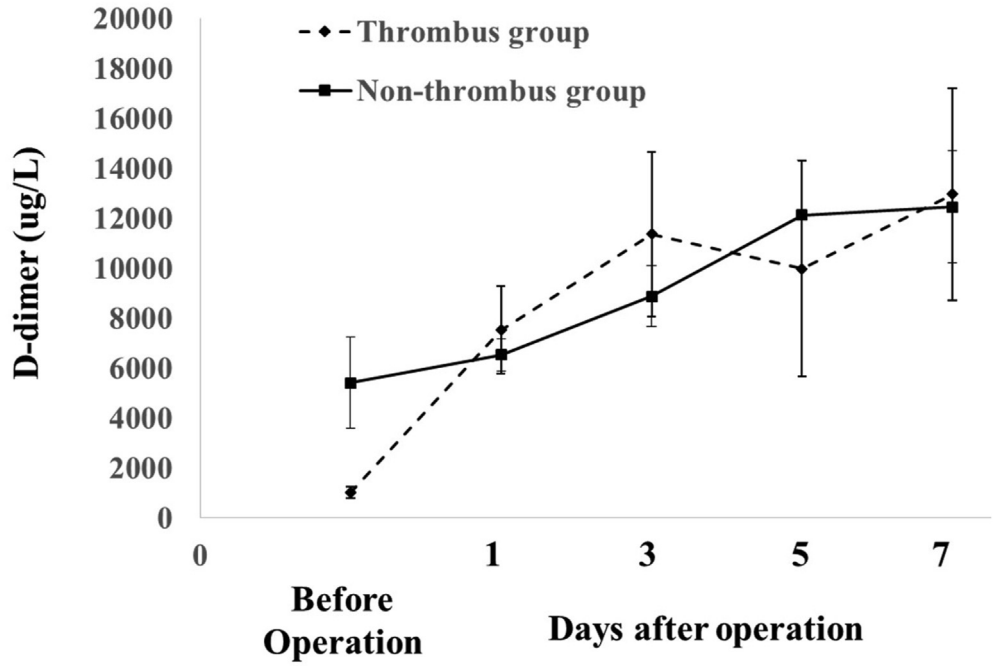

Figure 3. The serum D-dimer levels (μg/L) following splenectomy did not differ significantly between the 2 groups ($P > 0.05$).

variables. All tests were two-sided, with a P value of <0.05 considered statistically significant.

Declarations

Author contribution statement

Qiang Wei, MD: Conceived and designed the experiments; Wrote the paper.

Shengmin Mei: Analyzed and interpreted the data; Wrote the paper.

Zhifei Fu; Chengzuo Han; Xiaodong Wang: Analyzed and interpreted the data.

Jun Chen; Peng Liu: Contributed reagents, materials, analysis tools or data.

Bin Chen; Xin Fang; Changku Jia; Shusen Zheng: Performed the experiments.

Xiao Xu: Conceived and designed the experiments.

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Data availability statement

Data included in article/supp. material/referenced in article.

Declaration of interest's statement

The authors declare no conflict of interest.

Additional information

No additional information is available for this paper.

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